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# BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

VOLUME LIII, NUMBER 5

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November, 1933

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

*Made in United States of America*

# BULLETIN
## OF
# THE JOHNS HOPKINS HOSPITAL

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*Twenty-five reprints*, with covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

*Correspondence concerning business matters* should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

*This periodical is issued monthly.* Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

*Subscription price.* In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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Agents for the British Empire, except Canada: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, W.C. 2, London.

## THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918

*Photograph by Bachrach*

UNIV. OF MICH.

# Frederick Henry Baetjer

## 1874–1933

Frederick Henry Baetjer, pioneer investigator in the diagnostic and therapeutic use of the roentgen ray, died at his home in Catonsville, July 17th, 1933. He was born in Baltimore, Maryland, on August 7th, 1874, the son of Henry and Fredericka Baetjer; his preliminary education was in the public schools of Virginia and the Shenandoah Valley Academy. He received his A.B. from the Johns Hopkins University in 1897 and his M.D. in 1901, serving his interneship at the Johns Hopkins Hospital. Following this he took a post-graduate course at the University of Berlin, and in 1903 returned to the Hopkins and organized the Department of Roentgenology at that Institution. He devoted his entire life to the development of this Department, serving successively as Assistant, Associate and Associate Professor until 1921, when he was appointed Professor of Roentgenology. In 1903, he married Mary Yarnall Carey, who with one daughter, survives him.

Dr. Baetjer was a member of the Medical and Chirurgical Faculty of Maryland and the American College of Radiology. As a delegate he attended the meeting of the International Roentgen Ray Society at Amsterdam in 1908. He was a member of the American Roentgen Ray Society and was elected president of this Society by his colleagues in 1911. He was consultant roentgenologist to the Union Memorial Hospital, The Church Home and Infirmary, The Hospital for the Women of Maryland and the Children's Hospital School. After the entrance of the United States into the World War he served as a Major in the Medical Corps of the United States Army, and during his service assisted in the editing of the United States Army X-ray Manual.

Dr. Baetjer worked untiringly to have roentgenology put on a sound scientific basis, and was vastly more interested in the diagnostic and interpretative than the technical side of the X-ray. He always insisted that the X-ray findings had to be taken into consideration with the clinical findings before a flat diagnosis could be made. He was a brilliant teacher, and not only students but many doctors at-

tended his Diagnostic Clinic. His opinion in regard to any abnormal change noted in an X-ray plate was priceless and many films were sent to him by doctors throughout the country for his interpretation. He often jokingly remarked that he believed he could carry on a practice by mail.

Of his contributions to medicine probably the most significant is his book on the diseases of the skeleton of which Dr. Waters was co-author. This book was in no sense a compilation. It reflected Dr. Baetjer in its every line, and presented his opinions on, and recorded his personal experience with the subjects under discussion, departing in many instances from the accepted point of view of roentgenology at the time of its publication.

Since Dr. Baetjer began to work with the X-rays in their early days when the need for protecting the operator was unrealized, he suffered many injuries to his hands and eyes, which necessitated his undergoing numerous palliative operations. In spite of this, Dr. Baetjer worked on and on, most tenaciously and courageously, to combat the many obstacles that confronted him from time to time. His jovial disposition won for him hosts of friends and he always enjoyed telling or listening to a good story.

A most glowing tribute was paid to Dr. Baetjer by the late Dr. William S. Thayer, Professor Emeritus of Medicine at the Hopkins, when he presented a portrait of Dr. Baetjer to the University on February 22nd, 1932, its Fifty-sixth Commemoration Day. This tribute seems to contain all that one could say about Dr. Baetjer, the man whom we loved so well and whom we shall so sadly miss. It reads in part: "Who is more universally loved than Baetjer? A singularly alert and engaging figure, interested in clinical medicine and surgery, he was one of the earliest to devote himself to the applications of the then new roentgenology diagnosis. . . . . Endowed by nature with an unusually acute, lucid, logical mind . . . . he has become a diagnostician of rare ability, a recognized leader and an unsurpassed teacher in his special field. . . . . "

Dr. Baetjer gave of himself most unselfishly that coming generations might be benefited. He could, in Kipling's words, "meet Triumph and Disaster and treat those two impostors just the same." May the results of his work live on for years and inspire others to follow in his footsteps.

# LATE CONGENITAL SYPHILIS[1]

## A Study of the Results of Treatment in 267 Patients

FRANK R. SMITH, JR.

*From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital*

Submitted for publication July 1, 1933

*Introduction.* There are comparatively few modern reports in the extensive literature of congenital syphilis which deal with the end results of treatment in the late form of the disease. Enough evidence is available to indicate that in infantile hereditary syphilis, provided the child survives, treatment is successful in accomplishing clinical, serological, and probably biological "cure" in a large proportion of patients. It is generally believed, however, that in late congenital as in late acquired syphilis these aims are less readily achieved; there is some doubt as to the possible correlation between clinical and serological "cure"; and the optimal amount of treatment is undetermined. It is the purpose of this paper to fill in a portion of this gap, and to study some factors which appear to be responsible for the successes or failures of treatment.

The material consists of 462 patients seen in the Syphilis Clinic of the Johns Hopkins Hospital, which enrolls only patients over the age of 13 years. Infants and younger children are cared for in the Pediatric Clinic. In a few cases of this series, the records of the Pediatric Clinic have been utilized, when the child had started treatment in that division or had been followed there into adolescence.

*Race, Sex, and Age Distribution.* The data as to race and sex show curious differences from the race and sex distribution of patients with acquired syphilis in our clinic (Turner) (1). Among our adult syphilitic population, only 34 per cent are white, and 49 per cent are females. In this group of late heredosyphilitics, 56 per cent are white and 59 per cent female. This suggests that untreated (and usually unrecog-

[1]This investigation has been aided by grants from the Milbank Memorial Fund and the United States Public Health Service.

nized) congenital syphilis is responsible for a higher mortality in infancy and early childhood among negroes than among white patients, and among males than among females.

The mean age at the time of admission to the clinic was between 14 and 15 years for white males and females, and for colored males, but was three years higher for colored females. The explanation of this race and sex difference is not clear. A considerable number of patients were over the age of 25; these are being made the subject of special study.

*The Relationship of Lesions to Race and Sex.* In view of the many excellent studies of the lesions produced by late congenital syphilis

TABLE I

*The relationship of race and sex to the original lesion leading to admission*

| | | TOTAL PATIENTS | PER CENT OF PATIENTS SHOWING SPECIFIED LESION | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Ocular | Nerve deafness | Osseous | Neuro-syphilis | Other | Latent |
| White | Male | 115 | 40.0 | 4.3 | 12.1 | 3.4 | 6.0 | 25.1 |
| | Female | 143 | 33.5 | 3.5 | 16.8 | 3.5 | 4.8 | 37.7 |
| Colored | Male | 75 | 29.3 | 4.0 | 6.6 | 1.3 | 8.0 | 53.3 |
| | Female | 129 | 37.2 | 3.9 | 5.4 | 0.0 | 3.8 | 48.0 |

and of its stigmata, no attempt has been made to study these in detail in our material. The active lesions fall readily into five major categories:—ocular (overwhelmingly interstitial keratitis), osseous (including periostitis or osteitis of long or flat bones, arthritis, and synovitis), nerve deafness, neurosyphilis, and a varied small group, designated here as "other," including gummatous lesions of the skin, mucosae, or viscera. In addition, there is a large group of patients in whom the infection is latent, and recognizable only on the basis of stigmata, a positive blood Wassermann test, or both. When the race and sex distribution of these various groups is studied, as in table I, there are found several points of interest, in which the congenital differs from the acquired infection. Ocular lesions and nerve deafness occur with equal frequency in the two races and sexes. Osseous lesions, however, are more than twice as common in white patients as

in negroes, an exact reversal of the racial distribution in the acquired disease (Turner) (1). Neurosyphilis follows the same racial pattern as in acquired syphilis, *i.e.*, it is much more frequent in whites than in negroes (Turner); but contrary to its much higher incidence in males than in females in acquired syphilis (Moore) (2), the sexes are equally affected in this series. This same phenomenon has been pointed out by others (Schmidt-Kraepelin (3); Jeans and Cooke (4)). It can only mean that the factor which protects the female sex against the development of neurosyphilis is operative only in adult life, but not in infancy or childhood. This factor, whatever it may be, apparently protects against other lesions of syphilis as well, since latency is distinctly less frequent in the heredosyphilitic females of this series than in adult females with the acquired disease. To phrase this statement differently, though lesions of one or another sort develop less frequently in white patients with congenital and also with acquired syphilis than in negroes, they develop with equal frequency in the sexes in the congenital disease.

The congenital syphilitic, therefore, is more likely to develop some lesion at some time than the adult with the acquired infection; neither race nor sex confers protection against any type of lesion except those involving the nervous system or the bones. In contrast to what happens to the adult, these lesions are more frequent in whites than in negroes. These facts are not yet susceptible of interpretation; they are recorded in the hope that they may aid in the study of the fascinating problem of the relationship of human constitution to disease.

*History of Manifestations of Infantile Syphilis and their Treatment.* In not a single instance of this series, so far as we are able to determine, had the mother been treated for syphilis during the pregnancy which resulted in the birth of the syphilitic child. This is to be expected, in view of the fact that in the mean age of our patients was 15 years, and that the routine treatment of pregnant syphilitic women was not current practice when these patients were *in utero*.

In the majority (89.7 per cent) of our patients, a history of manifestations of infantile syphilis (histories obtained from parents) was completely lacking. This may indicate either that early lesions actually did not occur or that they were so insignificant that they were disregarded. The child was not recognized as syphilitic, therefore,

until the appearance of obvious late lesions or stigmata, or until a routine investigation was made on account of the presence of syphilis in other members of the family. In 7.9 per cent of the group, there was a positive history of infantile lesions, which, however, had been allowed to pass untreated. Only 9 patients (2.6 per cent) had ever been given any treatment for early congenital syphilis; one of these had received a short course of neoarsphenamine, the others only mercury by inunction for short periods. These data seem to justify two conclusions: first, that in late congenital as in late acquired syphilis, lesions tend to appear particularly in children in whom the infantile infection ran a mild and usually unrecognized course; secondly, that the treatment given for early congenital syphilis probably prevents

TABLE II

*Age of patients on admission, tabulated according to the main complaint*

| TYPE OF LESION | TOTAL | AGE OF PATIENTS ON ADMISSION, YEARS | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | 31+ |
| Ocular | 164 | 5 | 26 | 56 | 42 | 25 | 5 | 5 |
| Osseous | 50 | 1 | 13 | 17 | 8 | 3 | 6 | 2 |
| Nerve deafness | 18 | 0 | 1 | 2 | 5 | 3 | 5 | 2 |
| C.N.S. | 10 | 0 | 2 | 2 | 5 | 1 | 0 | 0 |
| Other | 25 | 4 | 2 | 9 | 4 | 3 | 1 | 2 |
| Latent | 195 | 12 | 52 | 54 | 48 | 18 | 7 | 4 |
| Total | 462 | 22 | 96 | 140 | 112 | 53 | 24 | 15 |

the subsequent development of lesions or stigmata in a high proportion of patients.

There is no apparent relationship between the type of late lesion manifest on admission and the presence or absence of a history of infantile syphilis or of treatment for it.

Further studies of the ultimate outcome in a series of patients treated for early congenital syphilis are planned to verify these conclusions.

*Age of Patients on Admission, Tabulated According to their Main Complaint.* In table II is recorded the relationship of age on admission to the complaint which necessitated medical advice. It is of considerable interest that the older the patients, the higher the incidence of some type of lesion. Latency occurs in 54 per cent of the

age groups 0 to 10 years, and decreases with advancing age, until after 31 years only 26 per cent are found with a latent infection. Interstitial keratitis occurs most often between the ages of 11 and 20; osseous lesions appear somewhat earlier, from 6 to 16 years; nerve deafness tends to develop later, between 16 and 20 years of age.

*The Blood Wassermann and Cerebrospinal Fluid in Late Congenital Syphilis.* In this series of patients, the blood Wassermann was positive before treatment in 92 per cent, negative in 8 per cent. This is a higher incidence with a negative Wassermann reaction than occurs in many other reports; the evidence of congenital syphilis was, however, clear in all these patients.

Examinations of the spinal fluid have been carried out routinely in 182 members of the group who are free from clinical evidence of neurosyphilis. The results have been classified, as suggested by Moore (5) for the acquired disease, in four categories according to the type of abnormality in the spinal fluid. Asymptomatic neurosyphilis occurred in 10 per cent of the patients tested, approximately the same incidence as was found in a larger series by Jeans and Cooke (4). It was less frequent in negroes than in white patients; but in contrast to experience in acquired syphilis, slightly more frequent in females than in males. This is confirmatory of the previous statement that sex does not protect infants and children against neuraxis invasion as it does for the adult.

The ultimate outcome of congenital syphilis in patients with asymptomatic neurosyphilis is of interest. Of the 18 patients with positive spinal fluids, 7 were retested two or more years after the original examination. All 7 remained clinically asymptomatic; in 4 the fluid had become negative, presumably because of treatment; and in 3 it was unchanged. Of the 11 patients whose spinal fluids were not reexamined, 8 remained clinically asymptomatic and 2 developed clinical signs of syphilis of the central nervous system which necessitated their being placed in institutions. Clinical signs of neurosyphilis were not observed to develop in patients with normal spinal fluids; and in 8 patients in whom the original fluid was negative, repetition of the examination, four to ten years later, still gave negative results. It is suggested, therefore, that in the late congenital as in the acquired infection, asymptomatic neurosyphilis indicates the probability of the

development of clinical neurosyphilis, while a normal spinal fluid is a practical guarantee against such a disaster.

*Methods of Treatment Employed in this Series.* In most patients we have employed an arsphenamine alternating with a heavy metal. Old arsphenamine (606) has been used as a rule, particularly in older patients; neoarsphenamine in many of the younger children, silver arsphenamine especially in patients with interstitial keratitis. Though sulpharsphenamine is given in the Pediatric Department it was not employed in this group of cases. Prior to 1925 the heavy metal was mercury by inunction; since that date, mercury has been almost completely abandoned in favor of the intramuscular injection of bismuth salicylate in oil. These drugs have been given by the continuous method, in alternating courses, the arsphenamine course of 6 to 8 weekly injections, the heavy metal course of 6 to 12 weeks. In many patients rest periods have been permitted. In congenital neurosyphilis, tryparsamide has been utilized (in older patients) and more rarely Swift-Ellis or fever therapy.

The duration of treatment was variable, depending on the coöperation of the patients or of their parents. In general, an attempt was made to continue treatment for a minimal period of two years.

In discussing the results of treatment, three categories have been arbitrarily established, in which a time rather than a dosage classification is employed. These are as follows: *inadequate*—less than 30 weeks of treatment, which means 15 or less doses of an arsphenamine, calculated for age and weight; *moderate*—between 30 and 50 weeks of treatment, with an equal proportion of doses of an arsphenamine and one of the heavy metal compounds; *adequate*—50 or more weeks of treatment.

## THE RESULTS OF TREATMENT

*Definitions.* The outcome of treatment is considered from the clinical as well as from the serological standpoint, but particularly from the former. The result is considered satisfactory, so far as the patient is concerned, if he is restored to physical health and maintained in this condition for an indefinite period of time, whether or not his blood Wassermann test is reduced to normal. In the following analysis, therefore, the outcome is classified under two headings:

*Ultimate clinical outcome satisfactory* indicates that symptoms (and often physical signs) were abated and that no clinical evidence of progression or relapse occurred. Included in this category are patients with irremediable stigmata, even though these be the corneal scars of a long previously active interstitial keratitis, or total nerve deafness.

*Relapse or progression* signifies the development of fresh lesions, usually inflammatory, in eye, ear, bone, or elsewhere, or the continued progression of degenerative lesions in the ear or nervous system. Instances are included, perhaps arbitrarily, of progressive mental deterioration in imbecile children, even though they were not paretic. The type of relapse or progression is indicated in the tabular summaries, mental deterioration appearing under the heading "other."

TABLE III

*Relationship of total amount of treatment to ultimate clinical outcome*

| TREATMENT | TOTAL PATIENTS | ULTIMATE CLINICAL OUTCOME SATISFACTORY | DEVELOPED RELAPSE OR PROGRESSION OF | | | | |
|---|---|---|---|---|---|---|---|
| | | | Osseous | Ocular | Nerve deafness | C.N.S. | Other |
| Inadequate | 122 | 102 (83.6%) | 1 | 3 | 2 | 5 | 7 |
| Moderate | 50 | 36 (72.0%) | 1 | 6 | 3 | 0 | 4 |
| Adequate | 95 | 73 (76.8%) | 2 | 12 | 1 | 4 | 5 |
| Total | 267 | 211 | 4 | 21 | 6 | 9 | 16 |

*The Group Studied.* In further discussion, the group is reduced to 267 patients who were observed for 2 years or more, many of them for as long as 15 years. Re-examinations were performed in most instances; a large number of patients were persuaded, through the efforts of members of the Social Service, to return for study after a long absence from the clinic; and the majority were personally observed. The material is analyzed from various standpoints.

*The Clinical Outcome as Related to Total Amount of Treatment.* These data, shown in table III, furnish a considerable surprise. The clinical outcome was equally satisfactory (allowing for statistical error) regardless of the total amount of treatment given. Relapse or progression occurred in 20.9 per cent of the entire group, and about equally as often in patients with long as in those with short treatment. This

leaves out of consideration the amount of treatment necessary to improve or heal the presenting lesion, which, as is well known, must often be very prolonged (*e.g.*, in interstitial keratitis or neurosyphilis).

Ocular relapse (interstitial keratitis) is the type most frequently observed; this occurred in 12 of 95 patients who had been treated for more than a year.

*The Relationship of the Original Lesion to the Ultimate Clinical Outcome.* In correlating the types of relapse or progression with the original lesion leading to admission it was found that they occurred most frequently in the same structure that was first primarily involved. Ocular relapse (or progression) was by far the most common in all types, being found in 10 per cent of those whose main complaint was interstitial keratitis and in 37.5 per cent of all the relapses. Of those with central nervous system involvement 8 out of 10 showed a progression in that system alone and none of the ten had a relapse in the osseous, ocular or auditory system, in contrast to the others, each of which showed two or more. Of the 25 patients whose main lesion on admission was osseous, 20 showed a satisfactory clinical outcome, two relapses occurring in the osseous, two in the ocular system; of 89 with primary ocular lesions, 65 had a satisfactory clinical outcome, with 9 ocular relapses, 4 cases of nerve deafness, 1 case of neurosyphilis and 10 of a miscellaneous type. Of the 9 whose main complaint was deafness the outcome in 5 was considered satisfactory, 2 progressions taking place in the eye and two in the deafness. Of the 115 latent cases, 106 belong to the satisfactory group, with a scattering in the relapses. The unaccounted for and miscellaneous group consists chiefly of those patients who showed mental deterioration, usually associated with epilepsy, already mentally defective on admission, without other clinical or serological evidence of neurosyphilis, whose course was steadily worse and who at the end of the observation period were in institutions or under special care.

*The Relationship of Age at Start of Treatment to Ultimate Outcome.* This analysis, not published in tabular form, indicated that the age of the patient at the time of starting treatment played no rôle in the ultimate clinical outcome. The results were equally satisfactory, in terms of the incidence of progression or relapse, when treatment was begun at any time after the second year of life.

*Relationship of Race and Sex to Ultimate Outcome.* Relapse and progression were more frequent in white patients (25 per cent) than in negroes (15 per cent); this is largely due to the fact that progressive imbecility, while perhaps no more frequent among whites, was at least more obvious. There are no sex differences; the ultimate result is as satisfactory in males as in females.

*Relationship of Time to Ultimate Outcome.* The Cooperative Clinical Group (6) has shown that in latent, but not in early acquired syphilis, the mere passage of time improves on the clinical results of treatment. In late congenital syphilis, on the contrary, this relationship is not so apparent (table IV). The results are as good at the end of two years of treatment and observation as they are much later. It is suggested,

TABLE IV

*Relationship of total observation period to ultimate clinical outcome*

| TOTAL OBSERVATION PERIOD | TOTAL PATIENTS | ULTIMATE CLINICAL OUTCOME SATISFACTORY | |
|---|---|---|---|
| | | Number | Percentage |
| *years* | | | |
| 2– 5 | 107 | 83 | 77.5 |
| 6–10 | 100 | 80 | 80.0 |
| 11–20 | 60 | 48 | 80.0 |

therefore, that the patient's own resistance against infection does little to augment the results of treatment.

*Deaths.* There were 20 known deaths in the series. Two of these patients died in the Johns Hopkins Hospital; information as to the remainder was brought to light by the Social Service. The mortality from all causes is surprisingly low, in a group of patients followed for such a long average period of time, and aside from the deaths due to juvenile paresis, there were none directly attributable to syphilis.

*Autopsies.* It had been hoped that important information regarding the cause of death in late congenital syphilis and the age at which it occurred might be obtained from a survey of the autopsy records of the Johns Hopkins Hospital. Among 4500 consecutive autopsies there were 189 deaths of congenital syphilitic patients, but in only 2 of these was the patient above the age of 4 years. It seems

clear that late congenital syphilis rarely if ever causes death in the absence of involvement of the central nervous system.

*The Blood Wassermann Response to Treatment.* It is well known that the blood Wassermann test is reversed to negative with difficulty in late congenital syphilis, or, to express it differently, the Wassermann fastness is a common phenomenon in this form of syphilitic infection. The Wassermann response to varying amounts of treatment

TABLE V

*Relationship of Wassermann fastness to clinical progression or relapse*

(Patients observed two years or more)

| END RESULT OF WASSERMANN REACTION | | TOTAL PATIENTS | ULTIMATE CLINICAL OUTCOME SATISFACTORY | DEVELOPED RELAPSE OR PROGRESSION OF | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Ocular | Osseous | C.N.S. | Nerve deafness | Other |
| Positive | Fast | 105 | 77 | 12 | 2 | 7 | 2 | 5 |
| | Reversed, but positive at end of observation | 27 | 22 | 1 | 2 | 0 | 0 | 2 |
| | Positive with treatment. Not done at end of observation | 30 | 28 (77.7%) | 0 | 0 | 0 | 0 | 2 |
| Negative | Always negative (here) | 17 | 12 | 4 | 0 | 0 | 1 | 0 |
| | Negative for 2 yrs. or more after treatment and at end of observation | 79 | 65 | 4 | 0 | 2 | 2 | 6 |
| | Negative at cessation of treatment. Not done at end of observation period | 9 | 7 (80.0%) | 0 | 0 | 0 | 1 | 1 |
| Total | | 267 | 211 | 21 | 4 | 9 | 6 | 16 |

in the 267 patients of this series indicates that there is little relationship between serologic reversal and the duration of treatment; persistent Wassermann positivity was as frequent in patients treated for a year or more (50.5 per cent) as in those treated for 6 months or less (49.1 per cent). Even in the 115 patients in whom Wassermann reversal was accomplished by treatment, there was subsequent serologic relapse in 27 and only in 79 patients of the total number (29.6 per cent) was permanent serologic reversal achieved.

It is essential, in view of these facts, to determine the relationship of Wassermann fastness to ultimate clinical outcome in late congenital syphilis. The duration of treatment in most places is based on serological reversal. Is it really essential to attempt the reduction of a persistently positive Blood Wassermann by prolonging treatment? This point is examined in table V, where the ultimate clinical outcome is compared with the serologic outcome, *i.e.*, the Wassermann reaction. When the material is studied in this fashion, it appears that a satisfactory clinical outcome, with freedom from progression or relapse, is obtained with equal frequency, whether or not the Wassermann becomes negative. In other words, Wassermann fastness in late congenital syphilis is not of unfavorable prognostic import for the patients' future course.

Indeed, in late congenital as in late acquired syphilis, persistent Wassermann positivity, during and after treatment, is much more likely to be an expression of the delicacy of the serologic tests, than an index of clinical or pathologic activity of the disease.

*The Results of Treatment in Special Lesions of Late Congenital Syphilis. Interstitial Keratitis (I. K.).* A study of the effect of treatment on the eye lesion yields little information not already available from the splendid reports of Carvill and Derby (7), and of Robinson (8). Our material is divided into two groups, on the basis of acuteness of the ocular inflammation. All patients are reported as acute (141 in number) in whom an active inflammatory process was apparent, no matter what its duration; as chronic, (72 patients) in whom activity had long since subsided, leaving corneal scars of greater or less density. The effect of varying amounts of treatment and of the tendency to develop has been studied in the groups. As might be expected, improvement occurs only in those patients with acute lesions; scars are irremediable or nearly so. Quite obviously, more than 6 months of treatment is necessary from the standpoint of maximum therapeutic benefit, though subsequent ocular relapse may occur with equal frequency regardless of the duration of treatment. When the acute interstitial keratitis was unilateral, it usually remained so. This may certainly be regarded as a result of treatment since, untreated, the disease is almost always bilateral.

Statistical surveys were undertaken to determine if the association

of interstitial keratitis with other lesions or stigmata had any bearing on the ultimate outcome, but with negative results.

*Nerve Deafness.* There is a current misconception that nerve deafness, either in acquired or congenital syphilis, is in some way related to neurosyphilis. In this series of patients there were 63 with nerve deafness (in only a few of whom, however, was this the main complaint). This was not associated with clinical evidence of neurosyphilis in a single instance; and of 33 in whom the spinal fluid was examined, abnormalities were found in only two. These facts constitute strong evidence that the lesion, whatever its nature may be, lies outside the nervous system.

The results of treatment in nerve deafness, are very far from gratifying. Hearing was improved in 6 (9.5 per cent), unimproved in 47 (74.5 per cent) and became progressively worse in 10 (16 per cent). These results are confirmatory of the opinion expressed by other investigators. Treatment seems to have little or no beneficial effect. This series of patients has been studied without the aid of the audiometer, and the reported improvement in 6 of them is based on subjective evidence only. It is perhaps worth noting that 4 of these 6 individuals have had prolonged treatment (more than a year). In a smaller number of patients studied by Ciocco and Weinstein (9) by audiometric methods, improvement was lacking in all. It is even questionable whether progressive loss of hearing may be arrested by treatment, though the present series suggests that this, perhaps, is possible.

*Osseous Lesions.* The bony lesions of late congenital syphilis are predominantly the chronic and symptomless saddle nose, sabre shins, and cranial bossing. Only 32 patients of this series had acute inflammatory lesions involving bones or joints. In none did the therapeutic problem present special difficulty.

*Neurosyphilis.* Since only 10 patients of this group showed clinical evidence of neurosyphilis, statements as to therapeutic outcome are not warranted. In general, it may be said that clinical benefit from treatment was less obvious than in patients with the acquired disease.

*Latent Congenital Syphilis.* The aim of treatment in latent congenital as well as in latent acquired syphilis is to prevent the development of lesions, and in particular such crippling ones as blindness and

deafness. This seems to have been accomplished in our patients, judging from the clinical outcome in 115 patients observed for 2 or more years. Only two of the group developed interstitial keratitis, and none nerve deafness. Incidentally, a little treatment was as efficacious in this respect as a great deal. Whether this apparent prophylactic effect is actually due to treatment or to the patient's own defenses is not clear, for it is not possible to be sure that lesions would have developed with greater frequency had no treatment been given.

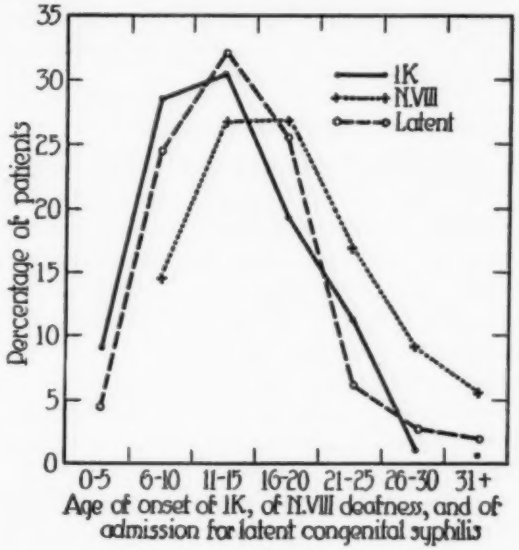


FIG. I

Some additional information as to this point may be gained, however, by comparing the age at onset of interstitial keratitis and nerve deafness with the age at which treatment was started (fig. I). The mean age at onset of interstitial keratitis in this series was 11.9 years, of nerve deafness, 16.9 years. In general, as fig. I shows, the patients of this group started treatment *before* the average age at which these lesions usually appear; that is to say, had no treatment been given, it is logical to expect that the lesions might have developed; and reasonable to conclude that treatment played some part in preventing them.

## DISCUSSION

The data presented in this paper indicate that the clinical arrest of late congenital syphilis, with or without obvious lesions, unless the nervous system is involved, may be accomplished with as little as 6 months of antisyphilitic treatment with an arsphenamine and a heavy metal; that the clinical results is the same regardless of whether the Wassermann becomes negative or not; and that the optimal amount of treatment depends largely on the disappearance of clinical signs and symptoms, varying between 6 months and 3 years. The response of the blood Wassermann may be completely disregarded as a guide to the type of treatment or to its duration.

## SUMMARY AND CONCLUSIONS

1. A study is presented of certain constitutional factors in 462 patients with late congenital syphilis and of the results of treatment in 267 of these patients who were observed for more than 2 years.

2. The race and sex distribution of this material suggests that congenital syphilis may be responsible for a higher mortality rate in infancy and early childhood among negroes than among white patients and among males than among females.

3. Congenital syphilis is less likely to remain latent than the acquired infection. Osseous lesions and neurosyphilis are more frequent in whites than in negroes; but in contrast to acquired syphilis, neurosyphilis is equally common in the two sexes.

4. Our material suggests that the lesions of late congenital syphilis tend to appear particularly in patients in whom the infantile infection has run a mild and usually unrecognized course.

5. None of our patients had received adequate treatment during the early stages of the disease.

6. The age at onset of different types of lesions is analyzed.

7. The incidence of asymptomatic neurosyphilis and its significance for ultimate clinical outcome is discussed.

8. The results of treatment are expressed chiefly in clinical terms, and are regarded as satisfactory if health is restored and maintained; unsatisfactory, if relapse or progression of syphilitic lesions occurs.

9. Various factors, such as the amount of treatment, the type of

original lesion, age at start of treatment, race and sex and the passage of time, are analyzed in relation to ultimate clinical outcome.

10. Late congenital syphilis is rarely a cause of death in the absence of neuraxis involvement.

11. Blood Wassermann fastness is frequent in late congenital syphilis; there is little relationship between the amount of treatment and of the Wassermann reaction reversal.

12. Wassermann fastness is not of unfavorable prognostic import from the standpoint of ultimate clinical outcome.

13. The results of treatment in special types of late congenital syphilis, *i.e.*, interstitial keratitis, nerve deafness, osseous lesions, neurosyphilis, are briefly described.

14. Nerve deafness in congenital syphilis usually occurs in the absence of other clinical or serological evidence of neurosyphilis.

15. Evidence is presented to show that treatment of latent late congenital syphilis prevents the subsequent development of interstitial keratitis or nerve deafness.

16. The relationship of these various facts to a plan of treatment for late congenital syphilis is briefly pointed out.

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# FOETAL BLOOD STUDIES

## IV. The Oxygen and Carbon-dioxide Dissociation Curves of Foetal Blood

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Foetal blood, both in its oxygen and in its carbon-dioxide relationships, differs considerably from that of the adult. It seems probable that these differences can be explained on a strictly physico-chemical basis and that they are conditioned by those laws which govern the diffusion of these gases through a wet membrane. In previous papers of this series such an explanation has already been attempted (1, 2). In doing so, however, it was necessary to assume, as a fundamental premise, that foetal blood takes up and gives off oxygen and carbon dioxide in the same manner as does the blood of the adult. While this would appear to be a reasonable assumption, it has seemed advisable to verify it, if possible, by making the present study of the oxygen and carbon-dioxide dissociation curves of normal foetal blood.

With the carbon-dioxide dissociation curves of various foetal bloods at our disposal, it has become possible to confirm and extend our earlier work on the carbon-dioxide tension of the foetal blood by means of a different and more direct procedure than we have hitherto used. This has consisted in interpolating upon the carbon-dioxide dissociation curve of a given blood its carbon-dioxide content as drawn, and in reading upon the abscissae of the graph its tension. Employing this method, a particular effort has been made in the present study to correlate the carbon-dioxide tension of the blood with the onset of respiration. If the partial pressure of this blood gas is the dominant factor in the onset of breathing at birth, it would seem likely that some optimal range of carbon-dioxide tension must exist which is particularly favorable for the onset of respiration and below

which only apnea is met. By recording the carbon-dioxide tensions of the foetal blood in a group of selected cases in which the first breath occurred as the blood was being taken, evidence will be brought to bear on this problem.

## PROCEDURES

Immediately after the birth of the baby, the umbilical cord was doubly clamped and umbilical vein blood was secured under anaërobic conditions, as previously described. This was used for the determination of the oxygen and carbon-dioxide content of the blood as drawn. The clamp proximal to the placenta was allowed to remain in place and following the delivery of this organ, a venepuncture was carried out on one of the large placental veins and a substantial quantity of blood, usually 50 or 75 cc., withdrawn for equilibration with various gas mixtures. The technique employed in the latter procedure was essentially that described by Dill (3), with minor modifications, the most important of which was the storage of the equilibrated blood in a closed sampling tube over mercury instead of under oil. The tonometers were of approximately 250 cc. capacity, 5 cc. of blood being introduced into each. In the oxygen dissociation studies, the tension of carbon dioxide in the tonometers was adjusted to 40 mm. of mercury ($\pm$ 2 mm.); the carbon-dioxide dissociation curves were determined, as is customary, with the blood completely saturated with oxygen. Equilibrations, as well as transfers of blood from tonometers to sampling tubes, were carried out in a large water-bath at a temperature of 38°C. The oxygen and carbon-dioxide contents of the blood were determined by the Van Slyke and Neill method in an apparatus of the portable manometric type, while the gaseous mixtures in the tonometers were analyzed in the Haldane apparatus. The formula used for calculating the gas tensions in the tonometers during equilibration was that recommended by Dill (3). To prevent lactic acid formation while the bloods were being handled and equilibrated, neutral sodium fluoride, in amounts of 10 mg. per cubic centimeter of blood, was used as an anticoagulant.

In estimating the carbon-dioxide tension of foetal blood by interpolating its carbon-dioxide content on the dissociation curve, it was necessary to correct each curve for the oxygen unsaturation of the

blood as drawn. In an example cited by Peters and Van Slyke, each volume per cent of oxygen unsaturation increased the carbon-dioxide capacity of normal adult blood by 0.4 volume per cent, the carbon-dioxide tension remaining constant (4). Our investigations of foetal blood, as shown in table I, indicate that each volume per cent of oxygen unsaturation increases the carbon-dioxide content by approximately 0.3 volume per cent. We have employed the latter figure. It should further be noted that in this part of the study we have plotted the carbon-dioxide dissociation curves on double logarithm paper; here, within the physiological range, the curves become practically straight lines (5), a circumstance which makes interpolation easier and more precise.

TABLE I

*Showing that foetal blood absorbs approximately 0.3 volume per cent more carbon dioxide for each volume per cent of oxygen unsaturation, the carbon-dioxide tension remaining constant*

| TONOMETER | | | BLOOD | | | | |
|---|---|---|---|---|---|---|---|
| Number | $CO_2$ tension | $O_2$ tension | $CO_2$ content | $O_2$ content | Diff. $CO_2$ content | Diff. $O_2$ content | Quotient a/b |
| | *mm. Hg* | *mm. Hg* | *vols. per cent* | *vols. per cent* | *vols. per cent* | *vols. per cent* | |
| 257 | 40.88 | 10.86 | 38.38 | 2.59 | 6.22 | 21.25 | *0.29* |
| 249 | 40.92 | 61.55 | 32.16 | 23.74 | (a) | (b) | |
| 249 | 42.54 | 41.55 | 32.59 | 20.39 | 1.20 | 3.83 | *0.31* |
| 255 | 42.43 | 58.84 | 31.39 | 24.22 | (a) | (b) | |

THE OXYGEN DISSOCIATION CURVE OF FOETAL BLOOD

It seems clear from figure 1, that the oxygen dissociation curve of foetal blood is similar in most respects to that of the normal adult blood reported by Bock, Field and Adair (6). Three slight differences, however, require mention. (*a*) At very low tensions the dissociation curve of foetal blood is characterized by a more striking S-deflection than in the normal blood; in other words, when the partial pressure of oxygen is low, foetal blood takes up less oxygen and gives off more of this gas to the tissues than the blood studied by Bock, Field and Adair. This fact may be of some significance from the viewpoint of tissue metabolism in asphyxia neonatorum. (*b*) At

high oxygen tensions, a similar condition is met, since adult blood attains a saturation of 95 per cent at a tension of only 75 mm. of Hg, whereas foetal blood requires an oxygen tension of 90 mm. for similar saturation. (*c*) Between these two extremes of oxygen tension,

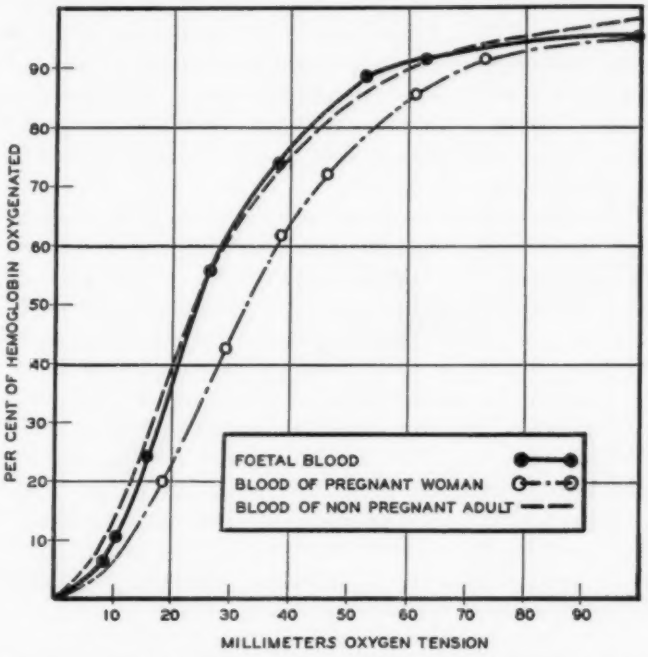


FIG. 1. SHOWING THE OXYGEN DISSOCIATION CURVE OF FOETAL BLOOD IN COMPARISON WITH THAT OF A NORMAL PREGNANT WOMAN AND WITH THAT OF A NORMAL NON-PREGNANT ADULT

The latter curve was taken from Bock, Field and Adair (6). The curve of the foetal blood was plotted from eight points and that of the maternal blood from seven points; curves almost identical with these were obtained from three other foetal bloods and two other maternal bloods.

however, the situation is reversed and in its middle ranges the curve of foetal blood becomes shifted slightly to the left; that is, at any given oxygen tension between 25 and 60 mm. of Hg, foetal blood takes up more oxygen than that of the adult.

The three differences which have just been cited between the curves of foetal and adult bloods are quite noticeable when the curve of Bock, Field and Adair is taken as a standard for adult blood. The first two differences, however, practically disappear when comparison is made with the oxygen dissociation curve published many years ago by Barcroft (7). Indeed, our foetal blood curve is practically identical with that of Barcroft with the single exception that it is shifted slightly to the left in its middle segment. It seems possible, therefore, that the behavior of the oxygen-dissociation curve of foetal blood at its upper and lower limit is not altogether specific for the curve of this blood.

When comparison is made between the curve of foetal bloo and that of the blood in pregnancy, a pronounced difference is noted, the latter curve being shifted definitely to the right. At any given oxygen tension between 25 and 60 mm. of Hg, accordingly, foetal blood takes up considerably more oxygen than that of the mother, its saturation being from 10 to 15 per cent greater. This characteristic of foetal blood seems to be quite constant at those gas tensions which are physiological for the foetus. It is an adjustment, furthermore, which is probably advantageous to the child *in utero*, for the foetal blood in passing through the chorionic villi can absorb more oxygen than could adult blood under similar circumstances. Conversely, the blood of the mother gives off oxygen much more readily than foetal blood; from the viewpoint of placental interchange, therefore, the dissociation relationships of these two bloods are ideal.

### THE CARBON-DIOXIDE DISSOCIATION CURVE OF FOETAL BLOOD

The carbon-dioxide dissociation curve of foetal blood follows a distinctly lower level than the curve of normal adult blood, as is shown in figure 2; it pursues, moreover, a somewhat lower course than the curve obtained from the blood of a normal pregnant woman. This circumstance, it may be noted, is just the reverse of that existing in the middle segment of the oxygen-dissociation curve. In other words, at most gas tensions foetal blood absorbs oxygen more effectively and at all gas tensions releases carbon dioxide more readily than does the blood of the mother. As already indicated, this state of affairs would greatly facilitate the placental interchange of these gases.

In so far as the foetal tissues are concerned, however, it would tend toward a low oxygen tension and a high partial pressure of carbon dioxide. This is in keeping with our previous finding that the carbon-dioxide tension in foetal tissues is normally high and suggests again that the foetal respiratory center, in particular, must have a diminished sensitivity to this gas.

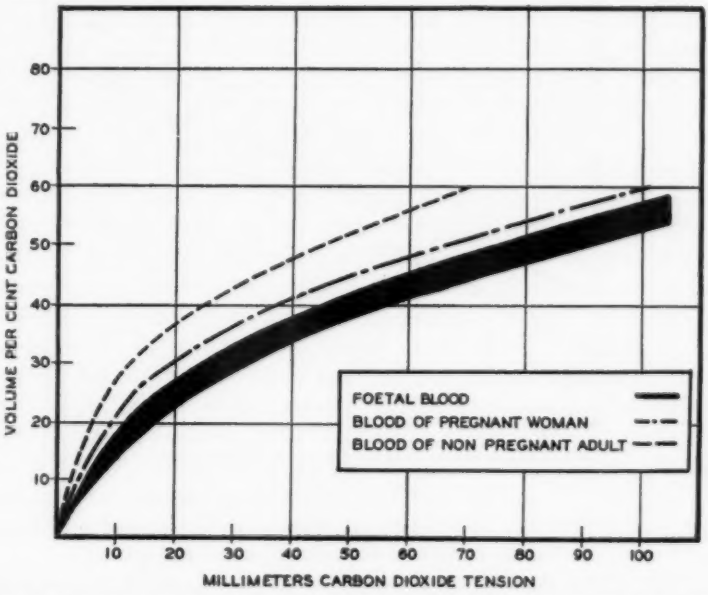


FIG. 2. SHOWING THE CARBON-DIOXIDE DISSOCIATION CURVE OF FOETAL BLOOD IN COMPARISON WITH THAT OF A NORMAL PREGNANT WOMAN AND WITH THAT OF A NORMAL NON-PREGNANT ADULT

The latter curve was taken from Henderson (9). The curve representing foetal blood is a composite one based on five normal foetal bloods.

It seems probable that the depressed level of the carbon-dioxide dissociation curve of foetal blood, in comparison with that of normal adult blood, is largely the result of two factors. In the first place, the total serum base of foetal blood, like that of the pregnant woman, is low. Whereas the serum base of normal adult blood is usually about 154.0 mM., that of foetal blood averages about 148.0 mM. (8). At a

blood pH of 7.35, this difference of 6 mM. would decrease the carbon-dioxide capacity of the serum by approximately 14 volumes per cent. Secondly, the large amount of hemoglobin in foetal blood would produce an effect in the same direction, since the total carbon-dioxide

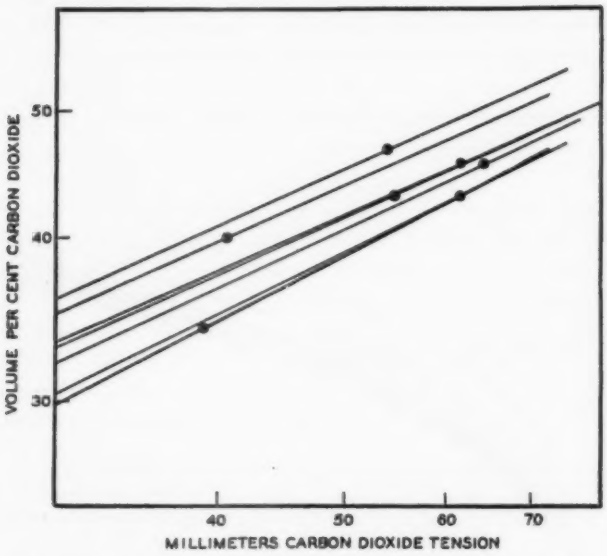


FIG. 3. SHOWING THE CARBON-DIOXIDE TENSION OF FOETAL BLOOD IN SEVEN CASES AT THE MOMENT RESPIRATION BEGAN

The carbon-dioxide content and the carbon-dioxide tension are plotted against one another on double logarithm paper, where the curves become almost straight lines. The cross on each curve represents the carbon-dioxide content of the blood as drawn; by referring this to the corresponding abscissa, the carbon-dioxide tension of the blood may be read. The curves are corrected for oxygen unsaturation on the basis that one volume per cent of unsaturation causes an increase of 0.3 volume per cent in carbon-dioxide content.

content tends to vary inversely as the hemoglobin concentration (4). However, for complete explanation of the carbon-dioxide dissociation curve of foetal blood, many other factors must be taken into consideration, such as its lactic acid content, its pH as drawn and its anion content. Evaluation of these factors would necessarily entail an

extensive investigation of the total acid base equilibrium of foetal blood, a subject which has been deferred for later study.

## THE CARBON-DIOXIDE TENSION OF FOETAL BLOOD AT BIRTH

In seven cases in which foetal blood was secured for carbon-dioxide dissociation studies, it so happened that the new-born child took its first breath just as the clamps were being applied to the umbilical cord. In figure 3 we have plotted the curves of these bloods (corrected for oxygen unsaturation) on double logarithm paper and have interpolated upon each curve the carbon-dioxide content of the respective blood as drawn. By reference to the abscissae it may be seen at a glance that the carbon-dioxide tensions of these bloods, taken at the moment respiration began, are scattered throughout the entire physiological range. Respiration began as readily and as vigorously at blood carbon-dioxide tensions of 38 or 40 mm. of Hg as it did when the tension was near 60 mm. We have thus been unable to establish any optimal range of carbon-dioxide tension particularly favorable for the onset of respiration. It would appear from these studies, indeed, that breathing may begin at any carbon-dioxide tension within the physiological range. This observation may permit of various interpretations, but it suggests, at least, that some factor other than the blood carbon-dioxide tension is the dominant one in the onset of respiration at birth.

## CONCLUSIONS

1. At gas tensions between 25 and 60 mm. of Hg, foetal blood absorbs oxygen more effectively than the blood of the mother.

2. At all gas tensions, foetal blood releases carbon dioxide more readily than the blood of the mother.

3. These two adjustments facilitate the placental interchange of these gases, but result in a low oxygen tension in foetal tissues and a high partial pressure of carbon dioxide.

4. At the moment respiration begins at birth, the carbon-dioxide tension of umbilical vein blood varies within wide limits, a circumstance which suggests that some factor other than the carbon-dioxide tension of foetal blood is the dominant one in initiating this phenomenon.

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# CLINICAL FEATURES OF THE CONTRACTED KIDNEY DUE TO PYELONEPHRITIS

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Submitted for publication July 1, 1933

If one has an opportunity to observe many cases of chronic Bright's disease, he will occasionally be surprised to discover that a patient, dying in uraemia as a result of what was supposed to be chronic nephritis of one of the usual types, has in reality, at autopsy, a bilateral pyelonephritis with shrunken kidneys and an irregularly dilated pelvis. Or, if one has an opportunity to watch many children through adolescence to middle life, he may remember the rare instance of a child with persistent pyelitis who died, when a young adult, in uraemia. There is little to be found concerning this particular form of pyelonephritis in textbooks or indeed in the English literature. A discussion of the matter is often omitted from the large treatises on Bright's disease, and is only touched upon in the textbooks on diseases of the genito-urinary system. Valléry-Radot, in the volume on the kidney in the *Nouveau Traité de Médicine*, refers to chronic forms of pyelonephritis with contracted kidney, but does not develop the subject in detail. Löhlein (1) was one of the first to recognize the significance of this form of kidney disease. In his article on *Schrumpfnieren*, in 1913, he separates quite clearly, as a special form of secondarily contracted kidney, the pyelonephritic type. He describes three cases in young women who died in uraemia. He notes that in two the blood pressure was elevated, and that the urine showed only moderate amounts of albumin with many leucocytes and no casts. Oberling (2), in an article on the classification of diseases of the kidney, states that from 10 to 15 per cent of all cases of chronic nephritis, thought generally to be hematogenous in origin are, in his experience, due to an ascending infection of the ureters and renal pelvis. He devotes some space to a description of the clinical course of this form of ne-

phritis. Secrétan (3) has also called attention to a form of chronically contracted kidney due to pyelonephritis. Gibson (4), in his Bradshaw lectures, gives an account of the origin and course of pyelitis and pyelonephritis. He distinguishes two forms of pyelonephritis: first, that following some gross obstruction in the urinary tract; and secondly, that in which there is no obvious obstruction to the outflow of urine. In the second category, in which we are interested, there were 72 cases, and in 11, or 15.4 per cent of these, an atrophic pyelonephritis was found. He describes the course of the disease in these cases. In most of them the blood pressure was elevated, but in some it was normal. The heart was hypertrophied in 4 out of 10 cases. There was a retinitis typical of chronic nephritis in one of 4 cases in which the eyegrounds were studied. If the process was active, the urine contained leucocytes, moderate amounts of albumin and bacteria; if the process was chronic, there might be only traces of albumin. The specific gravity of the urine was low. Schoen (5) has published an excellent description of the different forms of pyelonephritis from amongst the fifty instances of infection of the urinary tract observed in the Leipzig Clinic. More than half of them were dependent upon obstruction in the urinary tract which had resulted in the form of pyelonephrosis and pyelonephritis so familiar as a complication of prostatic disease or from gross ureteral obstruction. In 16, however, there was no known obstruction, and the process was so distinctive that he separates these as a special group. The disease, in these cases, had led to a form of chronically contracted kidney. Most of the patients were young women. The peculiar features were a history often of recurring infection of the urinary tract with lumbar pain; in the advanced stages elevated blood pressure, hypertrophy of the heart, elevation of the blood non-protein nitrogen[1] and death in uraemia; large amounts of urine, of low specific gravity, which contained small amounts of albumin and leucocytes but few or no casts or red blood cells; occasional attacks of fever, with tenderness on palpation of the kidney region and pyelograms that showed narrowing, or irregularities of the kidney pelvis with widening of the calyces.

Braasch and Cathcart (6) have made an extensive study of the

[1] Hereinafter referred to as N.P.N.

pyelograms in cases of pyelitis and pyelonephritis. They state that the pelvis of the kidney may show abnormalities, but that the ureters are particularly likely to exhibit points of obstruction or narrowing due to inflammation. Treatment was directed towards relief of these obstructions. Of 101 patients treated for 10 years, 44 were dead and 16 of these had evidently succumbed to some form of kidney disease. They call attention to the important fact that the average duration of life was 16 years.

Haslinger (8) has made an extensive study of the pyelonephritic kidney. Though he was particularly concerned with the unilateral form of pyelonephritis, he encountered 6 cases, amongst the 20 which he studied, in which the disease was bilateral. The unilateral form of the disease has also been described by Jacoby (9). It presents apparently a surgical rather than a medical problem, for the symptoms, when present, are usually referable to the local infection of the kidney, and the anatomical abnormality of the kidney is discovered chiefly by the use of pyelography. The most complete description of the pathological changes that are observed in bilateral pyelonephritis with contracted kidney (the form to which we desire to draw particular attention) is to be found in an article by Staemmler and Dopheide (10). They describe the appearance of the kidneys in five cases. The essential features are the inequality in the size of the kidneys, the gross irregularity of the surfaces, which often show knob-like projections, and the diffuse slight widening of the pelvis and thickening of the mucous membrane without signs of ureteral obstruction. Microscopically, the pelvis shows inflammation, with metaplasia of the epithelial lining; chronic inflammation and scar tissue in the medullary pyramids; an irregular projection of chronic inflammation into the cortex with disappearance of the parenchyma in these regions and contracting scars extending down from the cortex, with compensatory hypertrophy of the kidney parenchyma in small areas between the scars and inflammation.

Our attention was first directed to this interesting form of renal disease while studying a case of what was considered to be chronic Bright's disease in which several puzzling features were encountered. The patient (Case 5, J. D. No. 28917) was a young married white woman of 18, who was admitted to the Johns Hopkins Hospital on

January 19th, 1930, complaining of vomiting, headache, clouding of the vision and soreness in the back which had been present for about three months. The family history was unessential. She had been a delicate child with frequent illnesses—whooping-cough, measles, typhoid fever, double pneumonia, and with what was supposed to be malaria recurring for several years. At the age of 4, preceding the measles, she had difficulty in urination and had been told repeatedly by doctors since then that she had "bad kidneys." There had been one pregnancy in 1929 with miscarriage at 3 months. Her feet had been swollen at that time. About three months before admission she developed early morning headaches, vomiting, weakness, nervousness and mild dyspnoea. One month later her vision became clouded. There was frequent nycturia, rapid loss of weight, profuse leucorrhoea and soreness in the back for two weeks.

She was a small, emaciated, pale woman, with red hair, dry skin and without oedema. There was slight puffiness of the eyes and a subconjunctival haemorrhage on the left. The fundi showed an extensive haemorrhagic retinitis with swelling of the disc margins and vascular sclerosis. The heart was slightly enlarged (dulness 8.5 cm. in 5th space) and showed evidence of hypertrophy. Blood pressure 225/150. The heart rate was 104. There was slight abdominal tenderness most marked in the right lumbar region, and the left kidney was palpable. The extremities were emaciated. There was marked anaemia—Hb. 53%; R.B.C. 2,665,000, and a leucocytosis of 17,250, with 80% polymorphonuclear cells. The urine was pale, of low specific gravity, 1005–1012; there was no sugar, only small amounts of albumin, very rare hyaline casts, no red blood cells but many leucocytes. Cultures of the urine gave no growth. Blood N.P.N. was 88 mgm. per 100 cc., the urea clearance 12.5, 'pthalein 15%. It was thought that the patient was suffering from chronic vascular nephritis with impending uraemia, but the small amounts of albumin and the almost complete absence of casts seemed unusual.

The patient improved symptomatically, and left the hospital; but returned in April worse and obviously suffering from cardiac failure with oedema. In May she developed lumbar pain with fever, nausea, vomiting, leucocytosis and a distinct pyuria. The N.P.N. had risen to 140 mgm. per cent. An infection of the kidney was suspected and

pyelograms were made by Dr. Hunner. The bladder appeared normal. Cultures from the urine showed no growth. The pelvis of the left kidney was distorted and irregular, suggesting a congenital anomaly (fig. 3). She gradually grew worse. The blood pressure remained high, the urine showed only small amounts of albumin—0.05% to 0.1%. The blood N.P.N. rose, auricular fibrillation set in and the patient died on September 1st, 1930.

The autopsy (performed by Dr. Taylor) showed cardiac hypertrophy, small irregular lobulated kidneys with irregular dilated pelves (fig. 4), thickening of the mucosa and irregularity of the calyces. The urinary bladder was normal. There was no obvious obstruction of the urinary tract. Microscopically, there was inflammation of the pelvis. In the medulla and cortex large areas of inflammation alternated with comparatively normal islands of kidney tissue in which the glomeruli were quite well preserved, or with scars which extended in from the cortical capsule.

Since this time eight more cases of a similar condition have been observed. Some have not been diagnosed clinically, for they have been seen first in the terminal stage of the disease and have been recognized only at autopsy. We have gradually, however, become impressed with some salient features of the disease produced by the contracting kidney of pyelonephritis. This has enabled us to recognize, occasionally, the condition long before the terminal stage is reached. It has become evident that the process is of long duration, and advances slowly and insidiously over many years. It had probably and in some instances certainly existed in six patients for 3, 5, 8, 11, 16 and 17 years, respectively. One boy of 19 (Case 3) had been known to have pyelitis for 16 years, and one woman (Case 9) had had pyelitis complicating typhoid fever 17 years before her death.

The majority of the patients (7 of the 9) have been women. The disease reached its advanced stage in comparatively young individuals. Four of the patients were between fifteen and twenty years of age, four between twenty and thirty, and one thirty-six years of age. All nine patients were white.

Although the process is of long standing, the symptoms which may precede those associated with the prolonged terminal stage of renal failure are often slight and usually vague. Most frequently there is a

history of rather poor health extending over many years with repeated febrile illnesses ascribed to different causes. Occasionally there is a story of indefinite attacks of lumbar pain during which there may have been fever or cloudy urine. More often one obtains the history that an objective examination, made during childhood or adolescence, has shown some abnormality of the urine, such as the presence of albumin or pus.

The majority of cases, however, have not come under observation until there had developed some symptoms directly referable to the advancing renal failure. Headache, nausea and vomiting, loss of weight, lassitude, dyspnoea, epistaxis, lumbar pain, or in a few cases convulsive seizures were the most important symptoms that led the patient to consult a physician.

When most of the patients first came under observation, therefore, the signs of more or less advanced renal insufficiency were present. Some loss of weight and dryness of the skin were usually present. Anaemia, often of a severe grade, was observed in all but one instance. Oedema was rare unless, in combination with an enlarged heart, there were evidences of cardiac failure. This occurred in only 4 of the 9 patients. It was observed that the disease might run its entire course, apparently, without enlargement of the heart and without elevation of blood pressure. In four of the nine cases the blood pressure was normal, in five it was elevated, sometimes to a marked degree. The heart was demonstrably enlarged in all of the latter patients, and in one other in whom the signs of mitral stenosis were present. Retinitis with haemorrhagic exudates was observed in 4 patients. Abdominal or costo-vertebral tenderness was noted in several patients, and 3 patients (Cases 1, 2 and 5) had attacks of lumbar pain which were accompanied by fever, leucocytosis and pyuria. In one patient (Case 9) there was an ulcerative cystitis which caused profuse and persistent haematuria.

In the presence of symptoms and signs indicative often of advanced renal failure, the condition of the urine almost always attracted attention. It presented much the same characteristics in all cases except one (Case 9). The amounts were usually large, the specific gravity fixed at a fairly low figure varying usually between 1006 and 1012. The amounts of albumin were small, for often only moderate traces

could be found. Leucocytes were almost always present in considerable numbers, and at times there was actual pyuria. Casts were absent or present only occasionally in small numbers. They were almost always of the hyaline variety. Red blood cells were rarely if ever found. One patient showed gross haematuria from ulcers in the bladder mucosa; two showed red blood cells in the late stage.

Cultures of the urine frequently showed *Bacillus coli*. In 8 cases cultures were made on one or more occasions and in five a growth of *B. coli* was obtained.

The peculiar features of the urine, together with the occurrence of pyuria in relatively well defined attacks led to the examination of the bladder by cystoscopy, and kidney pelves by pyelography in five instances (Cases 1, 2, 4, 5 and 9).[2] The cystoscopic examination in all but one of these cases showed that the bladder was normal. In this one case, ulcers in the bladder were found. In some there was difficulty in passing the ureteral catheter on one or both sides. The pyelograms were distinctive, inasmuch as they showed irregularly deformed pelves, sometimes slightly dilated, with distorted, blunted calyces. In one or two instances the appearance led to the suggestion that the kidneys presented congenital anomalies.

The relatively slight changes in the urine became significant when contrasted with the evidences of serious renal impairment as measured by the functional tests. In 7 cases it was possible to determine the 'phthalein output. In four of these it was below 20 per cent. The non-protein nitrogen of the blood was elevated in all but one instance and in two cases it was above 200 mgm. per 100 cc. The urea clearance was determined by the method of Van Slyke in 7 cases. In all it was abnormally low and in four of these it was below 10% of the normal standard clearance. The $CO_2$-combining power of the blood was estimated in 3 patients, all of whom died in uraemia, and was found to vary from 23 vols. per cent. to 18 vols. per cent.

On the other hand, it was noticeable that the total plasma proteins were usually normal and that the ratio of the albumin to the globulin of the plasma was unchanged. The figures for many of the examinations are given in Table I.

[2] We are indebted to Dr. Hunner and his staff for these examinations.

## TABLE I

| NUMBER | PATIENT | COLOR | SEX | AGE | DURATION OF DISEASE | B.P. | BLOOD | | | URINE | | | | | N.P.N., MG. PER 100 CC. | PSTH., PER CENT | UREA Cl, PER CENT N. S. | $CO_2$, VOLS. % | PROT., GM. PER 100 CC. | A/G RATIO | RESULT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Hb. | R.B.C. | Lcts. | Sp. Gr. | Alb. | Lcts. | Casts | Culture | | | | | | | |
| 1 | M. F. | W. | F. | 24 | 5 yrs. | 146/90<br>162/106 | 85<br>78 | 4.4<br>3.5 | 10.2 | 1001–04 | +++ | +++ | 0–+ | B. coli | 42<br>50 | 60<br>50 | 42<br>34 | | | | Living |
| 2 | R. H. | W. | F. | 19 | 3 yrs. | 105/60<br>135/85 | 70 | 3.8 | 17.7 | 1004–06 | 0.1% | +++ | 0–± | B. coli | 37 | 55 | 23<br>54 | | 6.26 | 60/40 | Living |
| 3 | C. D. | W. | M. | 19 | 16 yrs. | 120/70<br>140/70 | 60 | 3.2 | 8.4 | 1006–12 | 0.1% | ++++ | 0 | Bacilli | 140 | 0 | 9 | | 6.16 | 61/39 | Living |
| 4 | H. S. | W. | F. | 21 | 7 mos. ? | 118/68 | 25 | 1.2 | 22.4 | 1010–15 | ++ | + | 0 | Neg. | 70 | 20 | 7.5 | | 5.75 | 41/59 | Living |
| 5 | J. D. | W. | F. | 18 | 14 yrs. | 225/150 | 44 | 2.1 | 26.8 | 1009–11 | 0.5% | +++ | 0 | Neg. | 130 | 5 | 3 | | 6.49 | 60/40 | Death. |
| 6 | M. L. | W. | M. | 24 | 9 mos. ? | 145/75 | 55 | 2.5 | 9.1 | 1008–09 | 0.3% | + | 0–± | Neg. | 312 | 0 | 2 | 23 | 6.81 | 58/42 | Death. |
| 7 | T. Mc.C. | W. | F. | 28 | 3 wks. ? | 170/110 | 35 | 1.9 | 18.8 | 1011 | ++ | + | 0 | B. coli | 250 | | | 20 | 5.78 | 53/47 | Death. |
| 8 | E. G. C. | W. | F. | 15 | 3 yrs. + | 120/80 | 41 | 2.5 | 12.4 | 1005–10 | 0.15% | +++ | 0 | | 1922, 74<br>1925, 168 | | | 18 | 7.32 | 60/40 | Death. |
| 9 | L. H. | W. | F. | 36 | 17 yrs. ? | 200/130 | 32 | 3.5 | 5.8 | 1005–1016 | 0.1–0.6% | ++* | 0 | B. coli | 40 | 40 | 40 | | 7.5 | 59/41 | Death. |

* Gross haematuria from ulcers in bladder.

The course of the disease, as has been observed, has varied somewhat.

Two of the nine patients (Cases 1 and 2) are living and actively engaged in work; two more (Cases 3 and 4) were known to be living a few months ago, but have not been seen recently. Five patients have died in uraemia.

Some of the significant features observed during the course of the disease are illustrated by the following cases:

*Case I.* (M. F., Hist. No. 28262.) A young white woman, aged 24, unmarried, was admitted to the Johns Hopkins Hospital on November 28th, 1929, complaining of headache, nose bleeds, fatigability and dry skin, which had developed during the last year. Her mother had died of heart disease, her father had died of "kidney trouble." She had never been very strong, having had frequent colds and tonsillitis, with occasional attacks of "grippe," but no serious illnesses. For two years she had had frequent nose bleeds. For one year she had had frequent headaches and undue fatigue. During a routine health examination an elevated blood pressure, and traces of albumin in the urine, without casts or red blood cells, had been found. She was well nourished, with dry skin, but slight pitting oedema over the shins. The retinal arteries were delicate but there was slight arterio-venous compression. The heart was not enlarged, the dulness 7.5 cm. to the left in the 5th space; the impulse was not forceful. There were no murmurs; the second aortic sound was loud. The blood pressure was 162/106. There was no costo-vertebral tenderness. The hemoglobin was 85%, the red blood cells 4,400,000, leucocytes 10,200. The urine was of low specific gravity 1001–1007. Albumin was present in from traces to 0.3%; leucocytes were numerous; there were very rare or no hyaline casts. The N.P.N. of the blood was 42, the urea clearance lowered to 42%, 'phthalein 60%. Cultures of the urine showed *B. coli*. Cystoscopic examination by Dr. Everett showed the bladder normal, the left ureter was not obstructed; the right ureter seemed to show some obstruction. Pyelograms showed an irregular distorted pelvis (fig. 1).

It was evident that the patient was suffering from a moderate degree of renal insufficiency with infection of the kidney pelvis. There was some hypertension without obvious disease of the retinal arteries.

The specific gravity of the urine was very low, but the small amounts of albumin and almost total absence of casts would have been unusual in Bright's disease. It was suspected, therefore, that the patient might have the contracted kidneys of pyelonephritis. During the three years that she has been under observation, there has been little progression of the disease. She has been regularly at work. The ureters have been catheterized and the kidney pelves drained. She has had occasional attacks of pain in the lumbar region, the blood pressure on 11/17/32 was 146/100, the 'phthalein on 11/17/32 was 40%. The N.P.N. on 11/17/32 was 40; and the urea clearance 33% of normal standard. The urine showed a specific gravity of 1004 to 1015, there were traces of albumin, no casts, and cultures gave *B. coli*. The significant features in this case are the accidental discovery of albuminuria in a young woman in comparatively good health, with moderate hypertension, attacks of pyuria, deformity of the renal pelves and definite evidences of impairment of renal function, which have been present for at least three years without an increase in symptoms.

It is remarkable to what extent the insufficiency of renal function may advance in many of these patients, without noticeable impairment of the health of the individual. Reference has already been made to the boy of 19 (Case 3), who was actively engaged in athletics, though there was no 'phthalein excreted in two hours, the blood N.P.N. was 130 mgm. per 100 cc. and the urea clearance 8% of the normal standard. There was as well, in this patient, an anaemia, for the haemoglobin was 60% and the red blood cells 3,200,000.

When serious symptoms of renal failure appear, however, the course is often very rapid and within a period of a few weeks the patient may die in uraemia. The following example is illustrative of the terminal phase of the disease.

*Case 6.* A young white man M. L. (No. 34560) of 24, was admitted to the Johns Hopkins Hospital on December 15th, 1930, complaining of pains in the back and severe headaches of 3 weeks' duration. His general health had been good. He had had scarlet fever at the age of 6. He had not had gonorrhea and had had no urinary disturbances. He had noticed nycturia for 9 months, without burning or discomfort, but with dull pain in the lumbar region. Three weeks before ad-

mission he had had cramps in his pectoral muscles, severe abdominal pain and vomiting. He had become very short of breath and weak. There was no oedema. He was a pale undernourished man with a yellowish pallor to his dry skin. The fundi appeared normal. The lungs were clear. The heart was slightly enlarged, the impulse forceful, 10 cm. from the midline in the 5th space. The heart sounds were loud. There was a systolic murmur at the apex. The radial arteries were palpable, the blood pressure was 145/75. The hemoglobin was 55%, the red blood cells 2,540,000, leucocytes 9,100. The urine was voided always in large amounts; the specific gravity was low and fixed at 1008–1009, contained small amounts of albumin, a few leucocytes, and on rare occasions a few hyaline casts. Cultures from the urine gave no growth. The 'phthalein was 0; the N.P.N. 116. The course was rapidly progressive. There were repeated vomiting, and frequent nose bleeds, with progressive anaemia, the haemoglobin reaching 38%, the red blood cells 1,820,000. The blood pressure fell somewhat to 125/82, the N.P.N. of the blood rose to 408 mgm. per 100 cc., and he died semi-comatose on January 12th, 1932, less than a month after admission. It was supposed that the patient was suffering from a chronic glomerular nephritis, though the elimination of large amounts of urine with such small quantities of albumin and the lack of casts and red blood cells seemed incompatible with this diagnosis. At the autopsy (performed by Dr. Dippel) the kidneys were small, unequal in size, and irregularly scarred and lobulated (fig. 5). The pelves were distorted but not especially dilated. There was no obstruction in the ureters. Microscopic examination, made by Dr. MacCallum, "shows an intense ureteritis, pyelitis and diffuse inflammatory reaction throughout the kidney. This together with extreme destruction of kidney substance suggests its origin as a chronic pyelonephritis." In addition to the bilateral pyelonephritis with contracted kidneys, there was a small tumor of the parathyroid glands with pathological calcification of the lungs, stomach and kidneys.

The course of the disease, as it progresses, may be modified by several circumstances. The patients in whom hypertension exists for a long period of time may suffer from symptoms of cardiac failure for a considerable period before the symptoms of uraemia supervene, while in others the evidences of cardiac failure may only be pronounced, as occurred in Case 5, during the terminal stages of the disease.

One patient (Case 8), a girl of 15, showed the retardation of growth and the changes in the bones which have been described as renal dwarfism. A description of this patient has been published by Lathrop (11).

The course of the disease was complicated in Case 9 by the occurrence of ulceration of the mucous membrane of the bladder which gave rise to persistent gross haematuria. Hypertension was a pronounced feature, the blood pressure ranging from 220/130 to 180/100. There was, on admission to the hospital, grave anaemia; and the patient suffered from considerable dyspnoea for 18 months before death. There was only moderate impairment in the renal function as estimated by the 'phthalein excretion, the elevation of the non-protein nitrogen of the blood and the urea clearance, until a short time before death. It is to be remarked that in this patient haemorrhages and exudates were not seen in the fundi.

Although the course of the disease may vary in certain particulars, depending on the activity of the infection of the kidney and pelvis, the degree and duration of the hypertension, the severity of the anaemia and the complications that may arise, there have been in this series of cases certain characteristics that recur with considerable uniformity. The long insidious course of the disease occurring most frequently in young women, the gradual loss of weight and dry skin; the peculiar features of the urine, with varying degrees of pyuria; the absence in most cases of the signs and symptoms of cystitis with the abnormalities of the pyelogram; the progressive anaemia; the remarkable evidences of renal insufficiency, and the sudden termination with or without hypertension in uremia appear to be the significant features of the disease. At autopsy the pathological picture is so characteristic that it is readily recognized. The bilateral lesions without gross obstructions in the urinary tract, such as may occur from renal calculi, tumors of the bladder, an enlarged prostate and stricture of the urethra, are significant.

The origin of the bilateral pyelonephritis in these patients is not altogether clear. Whether it arises originally as an haematogenous infection of the kidney, or as an ascending infection from the bladder cannot readily be determined at such a late stage of the disease. Bugbee (12) Chown (13) and Wilson and Schloss (14) have shown that

in a fair proportion of instances of pyuria in infants and children, small abscesses and foci of inflammation are found scattered through the kidneys. They regard the condition, therefore, not as pyelitis, but as a primary haematogenous infection of the kidney. Band, Dunlop and Dick (15) hold the same point of view and, furthermore, believe that the bilateral pyelonephritis of adults, of which they give excellent illustrations, arises in the same manner. From a study of the group of patients that we have observed, it would not be possible to draw any definite conclusion as to the mode of origin of the infection of the kidney. In one instance (Case 9) the process probably arose during the course of typhoid fever. In one or two instances there was a history of "pyelitis" during childhood. It might be suggested that the infection was of haematogenous origin in these patients. On the other hand, irregular dilatations of the ureters were observed in pyelograms made from other patients, and obstruction to the passage of the ureteral catheter was not uncommon. Points of narrowing in the ureters, particularly as they passed through the bladder wall, were noted in some instances at autopsy. Whether these changes are of primary significance or whether they occur as secondary phenomena consequent upon the long-continued draining of infected urine from the kidney cannot be determined. It seems probable, however, that such interferences with the free flow of urine from the kidneys may result in still further damage to the kidney, and it has seemed advisable, therefore, to catheterize the ureters of these patients at intervals, in an effort to establish free drainage from the kidney pelves.

It is to be remarked that the pyelonephritic contracted kidneys occur in young adults who are not the subjects of chronic cystitis or of gross obstruction to the urinary tract; that they are often bilateral and that the kidney pelvis shows only moderate and irregular dilatation, and sometimes only a moderate degree of inflammation. During the progress of the disease irregular portions of the kidney are slowly destroyed by inflammation, leaving other portions comparatively unaffected. Since the process is not a diffuse one such as occurs in glomerular nephritis, in the nephroses, or in arteriosclerotic Bright's disease, the patient may remain free of symptoms, except for those that are directly attributable to the low grade infection, during many years. The intact portions of the renal cortex, being comparatively

normal in structure and function, suffice for the needs of the individual under ordinary circumstances. The gradual reduction of this comparatively normal tissue sooner or later leads, however, to a restriction of kidney function, in much the same way as if portions of the kidney were being slowly amputated. When this reaches, eventually, a critical stage, advanced renal insufficiency with uraemia supervenes. The hypertension which was observed in about one-half of our cases might be dependent upon the reduction of renal tissue or possibly due to a concomitant arteriolosclerosis. The presence of retinitis, with changes in the retinal arteries, suggests that arteriolosclerosis might occur in some instances.

The actual cause of the infection is difficult to ascertain. In 5 of 8 of our cases *B. coli* was cultivated from the urine, but it is quite possible that this organism should be regarded as a secondary invader. It is noteworthy that in one case cultures from the urine gave no growth, and it is possible that in the late stages of the disease the organisms are not readily eliminated in the urine, or that the infecting organism has disappeared.

From the significant data that are now available, it should be possible to recognize this form of renal disease long before the critical stage has been reached in the destruction of kidney tissue. By doing so, one might hope through proper treatment to retard its progress or to arrest it altogether. In the latter event a partial cure might be effected. Our attempts to accomplish some results along this line have been largely directed to relieving any points of narrowing along the length of the ureters, in an effort to obtain as effective drainage as possible of the kidney pelvis.[3] At the present time it is not possible to estimate any benefit that may have been derived from this method of therapy, but we are inclined to believe that the renal function has improved slightly in two patients, and that the attacks of pyuria with lumbar pain in these two patients, who have been constantly under observation, have diminished in frequency.

In conclusion, it seems important to draw attention to these cases of bilateral pyelonephritic contracted kidney which are probably not very rare. Nine patients have recently come under observation, five of

[3] Patients have been referred to the Gynecological Clinic for treatment.

whom have died in uraemia and have been examined at autopsy. The disease occurred most frequently in women and was probably of long duration. The course may be characterized by attacks of pyuria accompanied by lumbar pain and sometimes by fever. In some patients the course may be practically symptomless until uraemia suddenly appears. In five of the nine cases there was hypertension, in four the hypertension was combined with haemorrhagic retinitis and arteriolosclerosis of the retinal vessels. There was rarely oedema unless cardiac failure occurred in the hypertensive cases. In all of the patients, dry skin, progressive anaemia and polyuria were present. There were no evidences of cystitis except in one patient. Pyelograms showed irregularities of various types in the size and shape of the kidney pelvis and calyces. The specific gravity of the urine was constantly low and the amounts of albumin small. Casts were rarely present; red blood cells were scarce or absent except in one patient with ulcers of the bladder. Evidences of impairment of renal function appeared sometimes years before death and occasionally progressed to a remarkable degree without serious symptoms. Death came in uraemia. The kidneys at autopsy were reduced in size, extremely uneven, scarred and distorted, and showed irregularly slightly dilated pelves which presented varying degrees of inflammation. Microscopically, areas of inflammation, or retracted scars running from the cortex, replaced large portions of kidney tissue. Between these areas the comparatively normal kidney tissue was irregularly disposed. There was no gross obstruction to the flow of urine. It is not clear whether the disease arises from a bilateral haematogeneous infection of the kidneys or from an ascending infection from the bladder. At the present time treatment has been directed towards obtaining adequate drainage of the kidney pelvis.

*Case I.* M. F., female, unmarried, Russian, *aet.* 24. (Unit No. 28262.)
Admitted to Johns Hopkins Hospital 11/29/29.
Clinical Diagnosis: Chronic pyelonephritis.

C. C. Nose bleeds for one year, headaches 5 months, fatigability 3 months, dryness of skin for 2 years, puffiness of eyelids.

F. H. Mother died at 42 of heart trouble; father living with "kidney trouble" for 7 years.

P. H. Never very strong; occasional attacks of tonsillitis; tonsillectomy in 1914, occasional attacks of "grippe," palpitation for years. No history of scarlatina, pneumonia, or rheumatic fever.

P. I. For about 2 years puffiness of eyelids, 14 epistaxes in last year, frontal headaches for 5 months, undue fatigue for 3 months. Blood pressure found elevated in routine examination 1 month ago; at same time albumin found in urine.

10/30/29. Tonsillectomy and telangiectases on nasal septum cauterized.

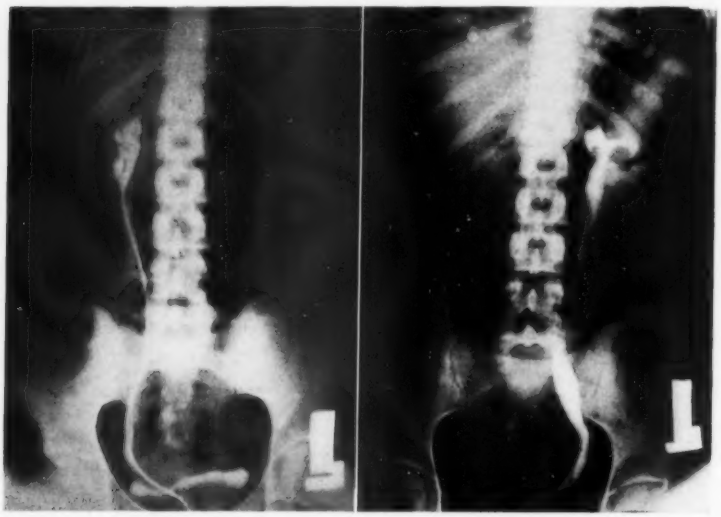

FIG. 1. CASE I. M. F. PYELOGRAMS OF RIGHT AND LEFT KIDNEY PELVES, SHOWING DISTORTION AND IRREGULAR DILATATIONS

P. E. T. 99.8°. P. 80. R. 20. B. P. 162/108.
Large, well nourished female, skin dry, conjunctivae injected, faint retinal oedema and slight tortuosity of retinal vessels. Lungs clear; Heart: maximum impulse not forceful, not enlarged, dulness in 5th space 7.5 cm. to left, 3rd space, 3 cm. to right, sounds clear, 2nd aortic somewhat accentuated, radial arteries not palpable. Abdomen soft, no costo-vertebral tenderness; liver, spleen and kidneys not felt.

12/12. Cystoscopic examination: Bladder normal, pyelograms (fig. 1) show irregular distortion of pelves and calyces. Wassermann negative.

11/17/32. The patient has been observed at frequent intervals for 3 years. Repeated dilatations of ureter and drainage of pelves have been done.

TABLE II

*Case I. M. F.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | Ca | Ph |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | *mg. per 100 cc.* | *mg. per 100 cc.* |
| 11/28/29 | 162/106 | 85 | 4.4 | 10.2 | 1001–1002 | + | ± | 0 | ++ | B. coli | 60 | 42 | | | 11.7 | 2.6 |
| 12/ 3/29 | 160/100 | | | | | | | | | | | 28 | 36, 49 | | | |
| 12/ 8/29 | 136/90 | | | | 1001–1007 | + | 0 | 0 | ++ | | 85 | 44 | | | | |
| 12/29/29 | 140/92 | 74 | 3.65 | 9.4 | | + | 0 | 0 | + | Staph. alb. | 50 | 50 | | | | |
| 11/29/30 | 144/95 | | | | 1010 | ++ | 0 | 0 | ++++ | | 45 | 42 | | | | |
| 2/27/32 | 160/112 | 78 | 3.5 | 8.9 | 1004–1013 | +++ | + | 0 | ++++ | B. coli | 45 | 44 | 30, 39 | 6.14 | | |
| 11/17/32 | 146/100 | 85 | 4.28 | 7.7 | 1004–1015 | + | 0 | 0 | ++++ | B. coli | 40 | 40 | 33, 33 | 7.05 | | |

The physical condition has remained practically unchanged, and except for occasional headaches and mild attacks of pain in the flanks at rare intervals, she has been symptomless and at work continuously. (See Table II.)

*Case II.* R. H., Female, white, single, *aet.* 19. (Unit No. 26,220.)
Admitted to J. H. H. Aug. 9th, 1929.
Clinical Diagnosis: Chronic pyelonephritis.
C. C. Yawning, "dopey feeling," duration 1 week.
F. H. Unimportant.
P. H. Usually well, measles, mumps, chickenpox, whooping-cough in childhood; rheumatic fever at 8; influenza and pneumonia at 9; occasional headaches. No urinary symptoms, no frequency. Albumin found in urine in routine examination.
P. I. For 2 wks. slightly listless and unduly fatigued; lost 10 lbs. in weight in one year. No other symptoms.
P. E. T. 99.8°. P. 80. R. 20. B.P. 105/60.
Well nourished, pale dry skin, no oedema, enlarged tonsils, lungs clear; heart dulness in 5th space 7 cm. to left, 3 cm. to right; sounds clear. Abdomen soft. Liver, spleen and kidneys not felt. Fundi normal.
8/15/29. Cystoscopic examination—bladder normal, no obstruction to ureters. Pyelogram of right kidney seems normal.
8/22/29. Tonsils removed and found to be grossly infected.
*Course of illness:* On several occasions during three and one-half years has had repeated short attacks of abdominal pain, fever and chills with burning on micturition and frequency. The ureters have been repeatedly catheterized, dilated, the kidney pelves drained.
5/1/31. Pyelogram left kidney shows evidences of pyelitis. She has been constantly at work and has felt well except for the attacks of abdominal pain and fever. (See Table III.)

*Case III.* C. D. Male, white, single, *aet.* 19. (Unit No. 44,850.)
Admitted to J. H. H. August 16, 1932; Discharged August 20, 1932.
Clinical Diagnosis: Chronic pyelonephritis.
C. C. "Kidney trouble;" transferred from Brady Urological Institute.
F. H. Negative. No history of renal disease.
P. H. Repeated attacks of pyelitis from 2½ to 8 years of age, characterized by chills, fever, albuminuria and pyuria. From 8 years of age to present time, asymptomatic and apparently healthy, participating actively in school athletics, but repeated observations revealed persistent albuminuria, pyuria and bacilluria. Studied and diagnosis verified at Harriet Lane Home and Brady Urological Clinic, Johns Hopkins Hospital, when 8 years old.

TABLE III

*Case II. R. H.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | | |
| 8/10/29 | 105/60 | 70 | 3.84 | 7.2 | 1010–1020 | 0.1% | + | 0 | ++++ | 0 | | 35 | | | | |
| 8/21/29 | 135/85 | 80 | 4.46 | 9.9 | 1012 | 0.025 | ± | 0 | ++++ | | 55 | 44 | | | | |
| 4/27/31 | 115/75 | 80 | 3.43 | 14.0 | 1004–1014 | ++ | ± | 0 | ++++ | B. coli | | 40 | | | | |
| 5/ 8/31 | 115/75 | | | 12.0 | 1007 | 0 | 0 | 0 | + | B. coli | | 38 | 28, 28 | 6.15 | 61/39 | Abdominal pain, fever and abdominal tenderness |
| 5/20–27/31 | 105/60 | 68 | 3.67 | 13.6 | 1006–1016 | 0.1% | 0 | 0 | ++++ | B. coli | 45 | 37 | 23, 21 | | | |
| 6/ 4/31 | 100/70 | | | 17.7 | 1007 | ± | 0 | 0 | + | | | 42 | 23, 23 | | | Recovery from acute attack |
| 11/21/31 | 105/68 | 78 | 4.2 | 12.2 | 1006–1015 | + | 0 | 0 | ++++ | | 60 | 36 | 42, 47 | 5.46 | 66/34 | |
| 6/27/32 | 115/70 | | | | | + | 0 | 0 | + | | | | | | | |

P. I. Returns to Brady Urological Clinic for routine examination; transferred to the Osler Clinic, J. H. H., for study.

P. E. T. 98.6°. P. 72. R. 20. B.P. 130/60.
Nutrition good; pallor with faint lemon-brown tint of skin, paleness of m.m. and finger-nails; fundi pale with diffuse shimmer and hazy disc margins. Lungs clear. Heart not enlarged, P. M. I. not forceful 7.5 cm. in 5th l. i. s.; sounds not accentuated, soft apical systolic murmur. Spleen and lower pole of right kidney palpable. Slight pitty oedema of tibiae and ankles.

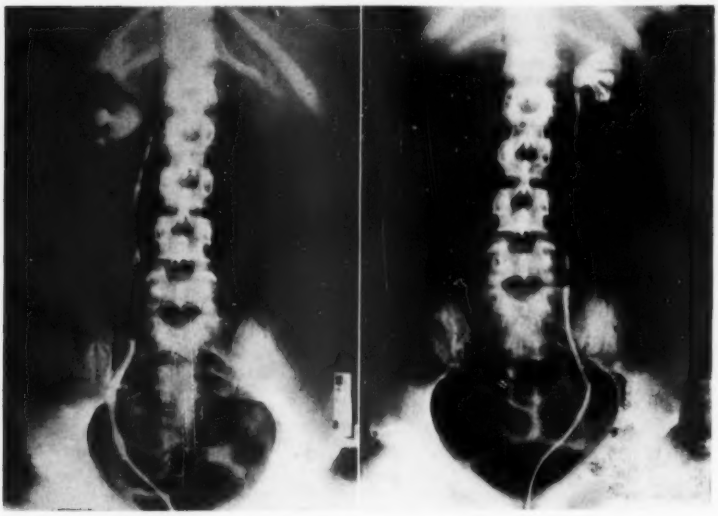

FIG. 2. CASE IV. H. S. PYELOGRAMS OF RIGHT AND LEFT KIDNEYS PELVES SHOWING DILATATION AND DEFORMITIES

*Course in hospital:* Temperature rose to 101.2° on second day of admission, patient felt moderately weak, and although parents were advised of patient's serious condition, he left the hospital against advice. (See Table IV.)

*Case IV.* H. S., Female, white, single, *aet.* 21 yrs. (Unit No. 44, 410.)
Admitted to J. H. H., July 14, 1932; Discharged August 14, 1932.
Clinical Diagnosis: Rheumatic endocarditis; Streptococcus septicaemia; Bilateral ureteral stricture; pyelonephritis.
C. C. "Pyelitis."
F. H. One brother has active pulmonary tuberculosis.

P. H. Never very strong. Pertussis at 4. Chorea at 5, followed by heart murmur; at 6, recurrence of chorea associated with symptoms of myocardial insufficiency necessitating restriction of activity for nearly 2 years. Mild exertional dyspnoea since. Tonsillectomy at 13. No sore throats. Loss of 22 pounds of weight past year.

P. I. Seven months ago cold with mild cough, fatigue, mild pain in both hypochondriac areas. 6 months ago severe general abdominal pain with fever. No chills, sweats or urinary symptoms. Gradual improvement; well in 3 weeks. 5 months ago severe pain in left flank radiating to left groin with cloudy urine; pain abated, but unfavorable progress with gradual loss of weight, strength, color, and development of nycturia. One month ago intravenous pyelography revealed enlarged right kidney and functionless left kidney, pyuria, slight fever (fig. 2). Bilateral dull ache in both flanks past 3 weeks.

P. E. T. 102.3°. P. 116. R. 16. B.P. 110/60.
Thin, pale, greyish pallor, signs of mitral stenosis and insufficiency, cardiac hypertrophy. No petechiae. Tenderness in right flank. Right kidney easily palpable. *Fundi:*—diffuse shimmer, engorgement of veins with faint arterio-venous nicking.

*Course:* Progressively unfavorable. Repeated ureteral dilatations and drainage. Constant fluctuating fever, pyuria, albuminuria and bacilluria. Anorexia, increasing weakness and pallor. One month after admission mild facial and pre-tibial oedema. Retina showed exudates and recent flame-shaped haemorrhages, some of which had white centers. Persistent tenderness in flanks. Progressive anaemia with leucocytosis. Last week of admission development of scattered petechiae. Blood culture showed growth of alpha streptococcus. (See Table V.)

*Case V.* J. D., Female, white, married, *aet.* 18. (Unit No. 28917.)
Admitted to J. H. H. Jan. 10, 1930. Death Sept. 1, 1930. Aut. No. 11,608.
Clinical Diagnosis: Arteriosclerosis; hypertension; uraemia; chronic diffuse nephritis; myocardial insufficiency; herpes labialis.

C. C. Nausea, vomiting, headaches 3 mos., clouded vision 2 mos., soreness in back 2 wks., inflammation of right eye 2 days.

F. H. Unessential.

P. H. Generally delicate, whooping-cough, measles, mumps as child; typhoid at 7 with double pneumonia; at 7 and 15 right-sided facial paralysis; malaria (?) as child for 14 years. No rheumatic fever, chorea or scarlatina. With measles at 4 yrs. difficulty in urination. Since has been told repeatedly that she had "bad kidneys." At 8 and 11, "hookworms." No headaches. Three attacks of tonsillitis; tonsillectomy in 1926. Miscarriage at 3 mos. in April 1929; feet swollen during pregnancy. June 1929, infection of right foot with swelling and fever for 6 days.

TABLE IV

*Case III. C. D.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp. Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | |
| 8/15/21 | | | | | 1010 | ± | 0 | 0 | +++ | B. coli ++ | 45 | | | | |
| 8/13–17/32 | 120/70 | 62 | 3.3 | 8.4 | 1001 | +++* | 0 | 0 | + | | 0 | 130 | 8 | 6.16 | 61/39 |

* 1.2 g./1.

TABLE V

*Case IV. H. S.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp. Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | |
| 7/14/32 | 110/60 | 60 | | 19.0 | 1015 | ++ | 0 | 0 | + | 0 | 20 | 52 | | | |
| 8/14–16/32 | 118/68 | 25 | 1.2 | 22.4 | 1010 | ++ | 0 | +++ | ++ | | | 70 | 7.5 | 5.75 | 41/59 |

8/12/32, blood culture positive for Streptococcus.

P. I. 3 mos. ago, headaches, nausea, weakness, lassitude, restlessness, mild dyspnoea and nycturia. 2 mos. ago clouding of vision with flames of light in eye. Loss of 20 lbs. in weight in 3 mos. Symptoms increasing in severity, soreness in back for 2 weeks.

P. E. Small, emaciated woman, pale, no oedema, dry skin, no dyspnoea. Haemorrhage in left conjunctiva. Optic discs swollen, oedema of retina partly obscuring arteries that are pale, tortuous and narrow, many

FIG. 3. CASE V. J. D. PYELOGRAM OF LEFT KIDNEY SHOWING IRREGULARITIES AND DISTORTIONS IN THE SHAPE OF PELVIS AND URETERS

retinal haemorrhages. Lungs clear. Heart slightly enlarged; P. M. I. 5th space 8 cm. from mid-line; systolic thrust. Dulness 5th space 8.5 cm. to left, 4th space 7.0 cm. to right. Sounds loud, 2nd aortic accentuated, protodiastolic gallop rhythm. B.P. 225/150. Pulse rate 104. Slight tenderness right lumbar region, and right kidney palpable. Spleen and liver not felt. Temp. 98° to 99°. Wassermann negative. Slight subjective improvement with discharge 3/1/30. Readmitted

April 19, 1930 with dyspnoea and orthopnoea. Temp. 100–101°. Heart increased in size, dulness in 5th space 11 cm. to left. Systolic murmur at apex with protodiastolic gallop. Blood pressure 180/150. Râles at bases of lungs. Liver palpable. Oedema of legs and feet.

5/17. Bilateral lumbar pain with nausea and vomiting. Indefinite mass in left lumbar region with pus in urine.

5/22. Cystoscopic examination. Bladder looks normal. Right ureteral orifice hidden by oedema; no obstruction in left ureter. Pyelogram left kidney (fig. 3) small distorted pelvis.

FIG. 4. CASE V. J. D. GROSS APPEARANCE OF KIDNEYS

5/30. Oedema and dyspnoea decreased. Tenderness in right lumbar region persists.

6/5/30. Discharged feeling better, but physical condition unimproved. Urinary output good, varying from 1000 to 1800 cc. on intake of 1500 to 3000 cc.

Readmitted July 25th, 1930, in very serious condition. Drowsy, twitching of muscles, dyspnoea with orthopnoea. Heart now much enlarged, dulness in 5th space 12 cm. to left; loud systolic murmur at base, accentuated 2nd aortic. Pulse 116. B.P. 200/146. Abdomen distended, liver palpable 10 cm. below costal margin, fluid wave in flanks, tenderness in lumbar regions. Oedema of optic discs very marked. During early August there was some symptomatic improvement, but later drowsiness, vomiting, dyspnoea and oedema increased; 8/31, heart becomes irregular, almost unconscious. Death Sept. 1st, 1930.

Autopsy 11608. Sept. 1, 1930 (Dr. Taylor).

Chronic cystitis; ureteritis and pyelitis; hydroureters and hydronephrosis. Chronic pyelonephritis with extreme contraction and scarring of kidneys. Cardiac hypertrophy. Chronic passive congestion of lungs, liver, spleen and pancreas. Ascites. Bilateral hydrothorax, oedema of feet and ankles. Haemorrhagic and diphtheritic ileitis. Enlargement of regional mesenteric lymph nodes. Chronic salpingitis. Old adhesions involving tubes and ovaries on both sides. Cysts in ovaries. Slight arteriosclerosis of aorta and coronaries (fig. 4). (See Table VI.)

*Case VI.* M. L., Male, white, *aet.* 24. Married. Pipe fitter. (Unit No. 34560.)

Admitted to J. H. H. Dec. 15, 1930; Died Jan. 12, 1931.

Clinical Diagnosis: Chronic diffuse nephritis (?); Pyelonephritis; Myocardial insufficiency; Uraemia. Death.

C. C. Pains in back, severe headaches, kidney trouble.

F. H. Unimportant.

P. H. General health good. Scarlatina at 6; measles, mumps and whooping-cough as a child. No diphtheria or rheumatic fever. Married 5 months. No urinary disturbances. No gonorrhea or syphilis.

P. I. Nycturia for 9 months with increasing frequency, with dull pain in lumbar region. Yellowish color to skin for 5 months. Severe headaches with epistaxis for 6 weeks. Three weeks ago pain in right pectoral region with severe abdominal cramps and dark stools. Shortness of breath for some time, so bad in last 3 weeks that he cannot walk a block without resting. No oedema, no haematuria.

P. E. Pulse 88. Temp. 98.6°. R. 20. B.P. 145/75.
Well developed, undernourished; pale, dry, yellow skin. Teeth bad, bleeding about gums; tonsils scarred. Optic disc margins indistinct, retinal arteries small; no retinal exudates or hemorrhages. Lungs clear. Heart not enlarged; P. M. I. forceful in 5th space 10 cm. from mid-line; dulness in 5th space 10 cm. to left; in 4th space 4 cm. to right; heart sounds loud, loud systolic murmur at apex; radial arteries palpable. Abdomen soft; liver and spleen not palpable. No oedema of extremities. Prostate normal. Wassermann negative. Throat culture shows no haemolytic streptococci.

*Course in hospital:* Slight improvement in headache and vomiting for a few days, but both soon returned. There was continuous bleeding from gums and occasional epistaxis.

12/17/30. Blood culture shows no growth. Electrocardiogram shows no abnormalities.

1/7/31. Blood platelets 520,000. The nausea, vomiting, weakness increasing. There is drowsiness. Oedema has never been present. The output of urine has been good; 1500 cc. to 2100 cc. on an intake of 2000 to 3000 cc. He grew steadily worse and died on Jan. 12, 1931.

TABLE VI

*Case V. J. D.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO | Ca | Ph |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Culture | | | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | | *mg. per 100 cc.* | *mg. per 100 cc.* |
| 1/11/30 | 225/150 | 53 | 2.6 | 17.2 | 1005–1012 | 0.3% | + | 0 | ++++ | No growth | 15% | 92 | | | | | |
| 1/17/30 | | | | | | | | | | | | 30 | 12.5, 13 | 6.49 | 60/40 | 10.6 | 6 |
| 4/19/30 | 180/150 | 54 | 2.6 | 26.8 | | 0.1 | + | 0 | ++++ | | | 104 | | | | | |
| 4/25–5/5/30 | | | | | | 0.1–0.05 | ±–0 | 0 | ++++ | | | 120 | 4.5, 4.5 | 4.68 | 48/52 | | |
| 7/26–9/1–30 | 200/146 | 44 | 2.1 | 10.3 | | 0.1–0.05 | ±–0 | 0 | +++ | No growth | | 156 | 3.01–3.4 | 4.88 | | | |

TABLE VII

*Case VI. M. L.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO | Ca | $CO_2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp. Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | | *mg. per 100 cc.* | *vols. %* |
| 12/15/30 | 145/75 | 55 | 2.5 | 9.1 | 1007–09 | +++ | + | 0 | ++ | Neg. | 0 | 116 | | | | | |
| 12/19–12/21 | 140/85 | | | | 1008 | + | ± | 0 | ++ | | | 202 | 1, 2 | 6.72 | 57/43 | | |
| 1/4–1/12/31 | 125/82 | 38 | 1.8 | 28.3 | | ++ | ± | 0 | ++ | | | 408 | | 6.81 | 58/42 | 11 | 23 |

Autopsy 11,797 (Dr. Dippel). January 12, 1931. Bilateral parathyroid tumor nodules. Extensive calcification of alveolar walls, bronchioles and venules in lungs. Lobular pneumonia. Extreme chronic nephritis with calcification of tubules. Hydroureter. Pyorrhea alveolaris. Microscopical examination made by Dr. MacCallum: "Shows an intense ureteritis, pyelitis and diffuse inflammatory reaction throughout the kidney. This together with extreme destruction of kidney substance suggests its origin as a chronic pyelonephritis" (fig. 5). (See Table VII.)

FIG. 5. CASE VI. M. L. GROSS APPEARANCE OF KIDNEYS

*Case VII.* T. McL. Female, white, married, *aet.* 28. (Unit No. 43103; Aut. 12,576.)

Admitted to J. H. H. May 2, 1932; Died May 6, 1932.

Clinical Diagnosis: Arteriosclerosis; hypertension; chronic vascular nephritis; uraemia; cardiac arrhythmia; complete heart block. Death.

C. C. Convulsions in past 2 days.

F. H. Negative; no history of tuberculosis, syphilis or renal disease.

P. H. Occasional convulsions up to age of 7. No scarlet fever, diphtheria, pneumonia, typhoid or rheumatic fever. Infrequent headaches. Occasional sore throats. Nycturia for 8 years. Marriage 8 years ago followed 10 months thereafter by delivery of 7 months' premature baby,

when doctor told patient she had Bright's disease. Another premature delivery 5 years ago; 3 years ago an induced abortion.

P. I. Three weeks before admission, severe cold with cough, soreness of chest, some sputum. Improved in week's time, but developed severe pain in back. Progressive loss of weight, anorexia and general malaise. Drowsiness and oedema of ankles for one week, followed by vomiting, oliguria and repeated convulsions.

P. E. T. 99.6°. P. 104. R. 20. B.P. 170/110.

Thin, pale, semi-stuporous, occasional twitching of shoulders, uriniferous odor to breath, some oedema lower back and tibiae; prominent eyes, right fundus normal; left fundus: arterio-venous compression, one small haemorrhage. Engorgement of cervical veins. Lungs clear to

FIG. 6. CASE VII. T. McL. GROSS APPEARANCE OF KIDNEYS

percussion and auscultation. Slight cardiac enlargement; dulness in 5th space 10.5 cm. to left, precordial bulge, lift, accentuated sounds with soft apical systolic murmur. Tenderness left lower quadrant, liver edge 4 cm. below costal margin. *Pelvis:* tenderness in left fornix. *Rectal:* mass on right side.

*Clinical Course:* One convulsion day after admission; temporary improvement following spinal puncture, but coma soon deepened, and death occurred in uraemia four days after admission.

Autopsy 12576 (Dr. Remsen). May 6, 1932. Chronic cystitis; ureteritis and pyelonephritis (B. coli); moderate generalized arteriosclerosis; cardiac hypertrophy; beginning arteriosclerosis in aorta and coronaries; acute tonsillitis; lobular pneumonia and abscess in right lower lobe; slight

diphtheritic colitis; subacute endocervicitis, gonococcal; blood cyst, left ovary; secondary anaemia; ascites, slight (fig. 6). (See Table VIII.)

*Case VIII.*[4] E. G. C., Female. White. Single. *Aet.* 15. Med. No. 53001. Admitted to J. H. H. April 6, 1925; Died May 14, 1925.

Clinical Diagnosis: Chronic nephritis; infantilism; uraemia; Death.

C. C. Drowsiness and anorexia.

F. H. No history of tuberculosis, syphilis or renal disease.

P. H. Youngest of 12 children, all living and well. Childhood diseases: pertussis, smallpox, measles, influenza, typhoid fever at 11, mumps at 13. No scarlatina, diphtheria, tonsillitis, or tendency to colds. Developed normally, though never robust; definite retardation of growth and physical development after typhoid fever at age of 11, although mental progress normal. Has never menstruated.

P. I. Two and a half years ago fatigability and drowsiness with B.P. 110/70, albuminuria discovered with rare granular casts. Course to admission marked by fluctuating weakness and drowsiness. One episode of headache, nausea and vomiting two years before admission. "Knock knees" noticed 2 years ago, of increasing severity. Palpitation and exertional dyspnoea for 1½ years; thirst, polyuria and nycturia for 1 year; anorexia and dull pain in left lower quadrant for one month.

P. E. Drowsy, well nourished, small of stature, skin coarse and dry, absence of secondary sexual characteristics, pasty pallor of face, puffiness of eyelids, uriniferous odor to breath, no oedema, marked genu valgum, beading of costo-chondral junctions, slight thickening of epiphyses of wrists. Heart not enlarged, 7 cm. to left of mid-line. No murmurs. The liver, spleen and kidneys were not felt.

*Clinical course:* Apparent improvement for few weeks, then progressively worse; development of brownish facial pigmentation, transient diplopia, nausea, increasing drowsiness, dyspnoea, lapsed into coma and died in uraemia.

Autopsy 8657 (Dr. Rich), May 14, 1925. History of renal dwarfism. Chronic pyelonephritis. Thickening of bladder mucosa and kidney pelves. Early lobular pneumonia. Hyperplastic marrow. Rickets. Diphtheritic laryngitis.

Note by Dr. MacCallum—"The kidneys are really reduced to mere sac like scarred masses of tissue with a few flattened prominent areas of kidney tissue which is recognizable as such. The ureters are extremely thick and so is the pelvis." (See Table IX.)

*Case IX.* L. H., female, white married, *aet.* 36. (Hist. No. 46850.)

Admitted to J. H. H. Dec. 11, 1932; Discharged Apr. 2, 1933; Readmitted Apr. 24, 1933; Died Apr. 29, 1933. Autopsy.

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[4] A complete discussion of this case with description of the pathological changes has been published by F. W. Lathrop, *Arch. Int. Med.*, 1926, **38,** 612.

TABLE VIII

*Case VII. T. McC.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Culture | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N. C.* | *gms. per 100 cc.* | |
| 5/2/32 | 170/40 | 35 | 1.9 | 18 | | ++ | 0 | ++++ | +++ | ++++ B. coli | 0 | 250 | | | |
| 5/3/32 | 160/70 | 50 | 2.2 | 37.8 | 1011 | ++ | 0 | + | +++ | | | 200 | | 5.78 | 53/47 |
| 5/5/32 | 130/60 | | | | | | | | | | | | | | |

TABLE IX

*Case VIII. E. G. C*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | Ca | Ph |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Cult. | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *mg. per 100 cc.* | *mg. per 100 cc.* |
| 11/ 2/22 | 110/70 | | | | 1.006 | + | ± (gran.) | | | | 11 | 74 | | |
| 2/20/24 | | | | | | + | | | ++ | | | 98 | | |
| 1/26/25 | | | | | | | | | | | | 161 | | |
| 4/ 6/25 | 119/60 | 41 | 2.5 | 12.4 | 1.008 | 0.2% | 0 | 0 | ++++ | | Tr. | 100 | 5.9 | 9.2 |
| 4/29/25 | 130/75 | 39 | 3.2 | 8.6 | 1.010 | +++ | 0 | 0 | ++ | | | 141 | 4.6 | 9.1 |
| 5/ 9/25 | 145/78 | | | | 1.006 | 0.2% | 0 | 0 | ++++ | | | 176 | | |

Clinical Diagnosis: Chronic bilateral pyelonephritis, ureteral strictures, chronic ulcerative cystitis, hypertension, hypochromic anaemia, uraemia, death.

C. C. Palpitation for 1 year; lassitude and oedema of ankles for 4 months.

F. H. Unimportant.

P. H. Chicken-pox, measles, pertussis, pneumonia and rheumatic fever as child; diphtheria at 15; subluxation of sacro-iliac joint at 18; acute fibrinous pleurisy at 18; typhoid fever with pyelitis and B. typhosus in urine at 20. Well since then. In 1914 and 1915 traces of albumin found in urine. No casts. Blood pressure in 1914, 1915 and 1916 varied from 100/70 to 120/85. No symptoms referable to urinary tract. Married 16 years. 3 children.

P. I. For one year dyspnoea on exertion; irregular nycturia, fatigability, anorexia, and palpitation, with gradual increase in symptoms. Four months ago suddenly became worse, grew sallow, became faint on slight exertion, very dyspnoeic, oedema of ankles appeared; menorrhagia was severe; symptoms steadily increasing.

P. E. T. 100 . P. 92. R. 22.

Very pale, orthopnoeic, showing loss of weight with pitting oedema of ankles. Fundi show oedema of retina, blurring of disc margins, tortuosity and increased light streak of arteries; no haemorrhages or exudates. Marked pyorrhoea. Forceful peripheral arterial pulsations. Lungs clear. Heart: precordial heave; P. M. I. forceful, in 5th space, 9 cm. to left of mid-line; dulness in 6th space 10 cm. to left; heart sounds loud with gallop rhythm and loud systolic murmur at base and soft systolic murmur at apex. Abdomen soft, liver just below costal margin, spleen and kidneys not felt, no costo-vertebral tenderness. Slight pitting oedema of ankles. Wassermann negative.

*Course of illness:* Rapid improvement in dyspnoea and disappearance of oedema on digitalis therapy. Slow increase in haemoglobin and red blood cells on iron ammonium citrate and liver therapy. Headache, nausea, vomiting and hypertension persist. On Jan. 19, 1933 showed gross haematuria. Through January, February and March the haematuria continued almost incessantly. Nausea was present for long periods at a time. Excruciating headaches were frequent; the blood pressure remained continually high.

Cystoscopic examination by Dr. Hurd on Jan. 19, 1933, showed ulcerations of the bladder with bleeding necrotic bases. On Feb. 9, 1933, ulceration of the bladder was still present, there was no obstruction, ureter and urine from left ureter showed no red blood cells, leucocytes or casts. On March 3, 1933, Dr. Hunner found slight obstruction to passage of ureteral catheter on right side. Pyelograms of right kidney showed dilatation of pelvis and calyces and dilatation of ureter.

At times, during February and early March, she was sufficiently well to be up in chair. By March 14, 1933, headache, nausea and lassitude had in-

TABLE X

*Case IX. L. H.*

| DATE | B.P. | BLOOD | | | URINE | | | | | | PHTH. | N.P.N. | UREA Cl | PLAS. PROT. | A/G RATIO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb. | R.B.C. | Lcts. | Sp.Gr. | Alb. | Casts | R.B.C. | Lcts. | Culture | | | | | |
| | | | | | | | | | | | *per cent* | *mg. per 100 cc.* | *per cent N.S.* | *gms. per 100 cc.* | |
| 12/10–12/32 | 230/140 | 29 | 3.1 | 5.4 | 1007 | +++ | 0 | +++ | + | B. coli, staph. | 60 | 36 | | 7.59 | 59/41 |
| 12/13–18/32 | 220/130<br>178/110 | 32 | 3.5 | 5.8 | 1010–1012 | 0.1% | 0 | + | ++ | | 50 | 48 | | | |
| 12/21/32–<br>1/3/33 | 160/100<br>190/120 | 73 | 4.7 | | 1010–1016 | 0.2% | 0 | + | ++ | | | 38 | 40 | | |
| 1/ 8/32–<br>1/23/32 | 180/120<br>200/120 | 70 | 3.7 | 7.9 | 1005–1012 | 0.4–0.6% | 0 | ++++ | ++ | B. coli | 40 | 34 | | | |
| 2/14/33 | 190/120 | 81 | 4.3 | 6.2 | 1010–1012 | 0.4–0.6% | 0 | ++++ | ++ | B. coli | | 40 | | | |
| 3/ 3/33–<br>3/27/33 | 180/110<br>206/130 | 80 | 3.9 | 13.1 | 1010–1012 | 0.4–0.6% | 0 | ++++ | ++ | | 30 | 53 | | | |
| 4/24/33–<br>4/26/33 | 90/84 | 82 | 3.4 | 11.0 | | | | | | | | 90 | | | |

creased. On March 23, the temperature which previously had not been elevated rose to 103°; she became drowsy and disoriented. Temperature persisted between 102° and 103° until she left the hospital on April 2, 1933.

Returned to Gynecological Service April 24, 1933, in semicomatose condition, showing emaciation, marked pallor, dry skin, slight oedema of ankles, and fever of 101°. There were no haemorrhages or exudates in the fundi. Examination of the heart, lungs and abdomen showed no essential changes from those noted previously. There was anuria and death in coma on April 29, 1933. (See Table X.)

Autopsy 13,124, April 29, 1933 (Dr. Kindell). Chronic pyelonephritis, chronic ureteritis and cystitis. Lobular pneumonia and oedema of both lower lobes. Apical scars and pleural adhesions both lungs.

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# THE PASSAGE OF ARSENIC THROUGH THE HUMAN PLACENTA FOLLOWING ARSPHENAMINE THERAPY

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Submitted for publication Aug. 9, 1933

A few years ago evidence was adduced in this Clinic that following the therapeutic administration of arsphenamine to pregnant women, arsenic is retained by the placenta for periods as long as fifteen days (1). It was furthermore noted that the retention of arsenic occurs chiefly in the foetal rather than in the maternal portion of the placenta, and the suggestion was advanced that this concentration of arsenic in the chorionic tissues acts as a barrier to prevent the passage of spirochetes from mother to child.

With certain limitations, this study served to explain the beneficial effect which arsphenamine therapy during pregnancy exerts upon the infant, particularly in cases in which treatment is begun early in gestation before the foetus has become infected with syphilis. But it is a well attested fact that the salutary effects of arsphenamine therapy upon the child *in utero* are not limited to those cases in which treatment is started early in pregnancy. Women with four plus Wassermann reactions are much more likely to give birth to non-syphilitic infants if they receive even as few as three or four injections of arsphenamine during the last trimester of pregnancy. According to Moore (2), even a single dose of arsphenamine administered late in pregnancy improves somewhat the prognosis for the child. Such observations are usually explained on the grounds that the child as well as the mother receives treatment from the maternal injections, and, since the foetal syphilis is in an early stage, it responds readily to the presence of the spirocheticidal agent. This explanation necessarily carries with it the implication that the administered arsphenamine, or one of its active decomposition products, is transmitted by the placenta to the foetal blood stream and thence to the foetal tissues. While this would seem to be a reasonable assumption, it has

heretofore been chiefly an inference drawn from clinical observations. As noted by Kolmer (3), definite knowledge concerning the behavior of the placenta in respect to the transmission of arsenicals is lacking. Does the human placenta, following arsphenamine therapy, transmit the drug to the foetus? If so, what proportion of the injected arsphenamine is received by the foetus? Is the process one of simple diffusion so that the concentration of arsenic in the foetal blood at all times approximates that in the maternal blood? Or, is some other mechanism involved?

It is the purpose of this paper to present evidence in answer to these questions.

## PROCEDURES

Neo-arsphenamine in dosages of 0.3 gram and arsphenamine in dosages of 0.2 gram were administered intravenously to 17 pregnant women at intervals varying from 9 minutes to 25 hours before the birth of the infant. At the moment of delivery blood was drawn from the mother by venepuncture on the opposite arm from that used in administering the arsphanemine. As soon as the child was born, the umbilical cord was doubly clamped and foetal blood drawn from the umbilical vein. The maternal and foetal bloods, in amounts of 10 cc., were then subjected to arsenic analyses, sodium oxalate being used as the anticoagulant. In six of the cases twenty-gram samples of the foetal portion of the placenta, minced and carefully washed of blood, were also analyzed for arsenic.

In eleven additional cases, in which a series of therapeutic injections of arsphenamine had been given to the mother during pregnancy, arsenic estimations were carried out on the meconium of the new-born infants during the first few days of life. In three of these cases, the foetuses succumbed for one reason or another, and it was possible to analyze also the liver and other foetal organs for arsenic.

All arsenic analyses were done by the Gutzeit method as described by Scott (4). The reagents employed were arsenic free, blank analyses showing no traces of arsenic. The Gutzeit method depends upon the evolution of arsine by the action of hydrogen on arsenic compounds under the catalytic action of zinc. The evolved arsine forms a brown compound when it comes in contact with strips of mercuric chloride

paper, and from the length and intensity of the color stain the amount of arsenic is estimated by comparison with standard stains. In our hands, the delicacy of the method has been such that, in a given sample of organic material, quantitative estimations could be made on 2 micro-milligrams (0.002 mg.) of metallic arsenic; since 10 cc. samples of blood were used, quantitative determinations were possible on bloods containing as little as 20 mmg. per 100 cc. With smaller concentrations of arsenic than this the stain on the mercuric chloride paper was yellow and was sometimes so faint that it could scarcely be detected by the eye.

The interpretation of these faint "traces" of arsenic in biological material is rendered peculiarly difficult by the fact that this element, in traces, is frequently (but not constantly) present in the blood and tissues of individuals who have received no therapeutic arsenicals whatsoever, its presence seeming to depend on the food, drink and environment of the person (5). We have noted similar traces of arsenic in the bloods of both mother and foetus in several cases in which no treatment with arsenic compounds had been administered. In the past, many investigations in this field have been invalidated because of failure to take into consideration this "normal" arsenic and because it has been assumed that traces of arsenic in blood or tissues were necessarily the result of injected arsphenamine. Accordingly, it has seemed advisable in the present study to disregard the occasional traces of arsenic met with. When we indicate, therefore, that the arsenic content of a given specimen is "none," we mean either that no trace of the element could be detected or that it was present in such minute quantities as to be indistinguishable from "normal" arsenic.

### *The arsenic content of foetal blood shortly after arsphenamine injections*

In the seventeen cases in which neo-arsphenamine and arsphenamine were injected into women shortly before delivery, the results were clear-cut and decisive. As is shown in Table I, the bloods of these women, taken at the moment of birth, contained large quantities of arsenic, particularly in those cases in which birth occurred within the first hour after injection. This was, of course, to be expected, for it is in keeping with the work of Fordyce and his associates (6), of

Kolls and Youmans (7) and of many others, upon the elimination of arsphenamine from the circulation. The seventeen foetal bloods, on the other hand, showed no evidence of arsenic. In view of the fact that the arsenic content of the maternal bloods at the time these infants were born was in several instances exceedingly high, the complete

TABLE I

*Showing the arsenic content of maternal and foetal bloods shortly after the intravenous administration of an arsenical to the mother*

In Cases 1 to 15 inclusive, neo-arsphenamine (0.3 gram) was used, while in Cases 16 and 17, arsphenamine (0.2 gram) was administered. The designation (T) indicates that a trace of arsenic, indistinguishable from "normal" arsenic (as has been discussed under "Procedures") was found. In Cases 1 and 6, delivery was accomplished by Caesarean section before the onset of labor.

| CASE NUMBER | DURATION OF PREGNANCY | WASSERMANN REACTION | INTERVAL BETWEEN INJECTION AND BIRTH | ARSENIC IN MATERNAL BLOOD | ARSENIC IN FOETAL BLOOD | ARSENIC IN PLACENTA | WEIGHT OF INFANT |
|---|---|---|---|---|---|---|---|
| | | | | *mmg. per 100 cc.* | *mmg. per 100 cc.* | *mmg. per 100 cc.* | |
| 1 | Term | Neg. | 17 min. | 640 | None (T) | 120 | 3,475 |
| 2 | Term | Neg. | 18 min. | 400 | None | | 3,370 |
| 3 | Term | Neg. | 19 min. | 340 | None (T) | | 2,870 |
| 4 | 9 Mos. | Pos. | 21 min. | 460 | None | 140 | 2,600 |
| 5 | Term | Neg. | 26 min. | 340 | None | | 3,300 |
| 6 | Term | Neg. | 33 min. | 500 | None (T) | 80 | 2,770 |
| 7 | Term | Neg. | 33 min. | 420 | None | | 3,080 |
| 8 | Term | Pos. | 35 min. | 400 | None | | 3,140 |
| 9 | Term | Neg. | 57 min. | 140 | None (T) | | 3,050 |
| 10 | Term | Neg. | 3 hrs. 9 min. | 60 | None (T) | | 3,000 |
| 11 | 9½ Mos. | Neg. | 3 hrs. 10 min. | 100 | None | 100 | 2,600 |
| 12 | 9 Mos. | Pos. | 3 hrs. 34 min. | 100 | None | 120 | 2,620 |
| 13 | 8 Mos. | Neg. | 4 hrs. 47 min. | 40 | None (T) | | 2,200 |
| 14 | Term | Neg. | 7 hrs. 43 min. | 60 | None | | 3,025 |
| 15 | Term | Pos. | 25 hrs. 22 min. | None (T) | None | 100 | 3,220 |
| 16 | Term | Neg. | 50 min. | 300 | None | | 3,450 |
| 17 | Term | Neg. | 9 min. | 450 | None | | 3,260 |

absence of the element in the foetal circulation seems surprising. It was at first thought that the failure of the arsphenamine to diffuse through the placenta might be due to some interference with normal placental interchange as the result of the uterine contractions associated with labor. That this was an incorrect supposition is shown by the fact that in the two cases in which a Caesarean section was done

before the onset of labor, (Cases 1 and 6), the results were precisely the same. But it may be objected that we are neglecting the traces of arsenic which were discerned in 6 of the 17 foetal bloods. As already noted, it seems reasonable to attribute these to "normal" arsenic. Even if it be granted that such traces are the result of the injected arsphenamine, they represent at the most quantities which are in the range of 5 mmg. per 100 cc. of blood. It will be observed that this is less than one hundredth the concentration of arsenic encountered in some of the respective maternal bloods. Certainly, it seems justifiable to conclude from these findings that arsphenamine does not pass through the human placenta by a process of simple diffusion, and if it does so at all, it must enter the foetal circulation in minute quantities and at a very slow rate.

*The arsenic content of the meconium following arsphenamine therapy*

The results just recorded suggest, of course, that the views long held in regard to "treating the foetus" by maternal arsphenamine therapy are based on a misconception. In consideration, however, of the strong clinical evidence in support of these views, it seemed desirable to follow the question further and to search in the foetus for arsenic in those cases in which the mother had had repeated arsphenamine treatments. Recalling that both arsphenamine and neo-arsphenamine are excreted in large measure through the bile, we felt that the foetal meconium, which is mostly bile, presented a unique opportunity for study in that it is retained in the intestines throughout pregnancy and should theoretically contain as an excretory product a considerable portion of any arsenic which had passed to the foetus. The arsenic content of the meconium in 10 cases in which prolonged treatment with arsphenamine had been given, together with other relevant information, is shown in Table II. These figures can leave no doubt that arsenic *does* pass to the foetus and is recoverable from the meconium in substantial concentrations. The amounts demonstrable in the meconium of t ıese cases varied considerably and seemed, moreover, to bear little relationship either to the total amount of arsphenamine which the mother had received up to the date of the last treatment. In addition to the amounts present in the meconium, it was

possible in one instance to show that the liver contained 12 mmg. of arsenic in a 10-gram specimen of tissue; since this liver weighed 135 grams, we may estimate that the entire organ contained approximately 160 mmg. of arsenic. In the maternal and foetal bloods of this series, as well as in the amniotic fluid of two cases, no arsenic which was definitely distinguishable from "normal" arsenic, could be detected.

## COMMENT

The fact that arsphenamine does not diffuse through the human placenta becomes readily understood when the nature of arsphenamine solutions is recalled. As was first clearly shown by Bauer (8) and confirmed and amplified by Raiziss and Gavron (9), arsphenamine behaves like a semicolloid. The drug diffuses very slowly through parchment and somewhat less slowly through collodion membranes. It resembles in many respects a protein and in the opinion of pharmacologists exists in solution in the form of rather finely dispersed molecular aggregates (10). Since the placenta is believed to be impermeable to all colloids, its behavior in respect to arsphenamine is characteristic. Moreover, as shown by Young (11), when arsphenamine is mixed with blood it enters into some sort of combination with a plasma constituent, probably globulin (12), and will dialyze from such a mixture very slowly or not at all. This circumstance would, of course, still further decrease the likelihood of this drug's diffusion through the placenta. In other words, the failure of arsphenamine to permeate the placenta is readily explained on the basis of colloidal chemistry and does not necessarily imply any "selective" or "vitalistic" activity on the part of that organ.

The mechanism by which arsenic (either in the form of arsphenamine or its decomposition products) does reach the foetus is less readily explained and at present must remain largely a matter of speculation. In this connection, however, it should be noted that the amounts of arsenic recoverable from the meconium are very small when compared with the quantities administered to the mother; they would not be in keeping with any massive diffusion of the drug from mother to child and suggest rather that the arsenical reaches the foetus in minute amounts. If the placenta holds back arsphenamine because it is a colloid, one would expect the drug to be filtered off as a residue

TABLE II

*Showing the arsenic content of the meconium, placenta, and foetal organs in cases in which the mother had had prolonged arsphenamine therapy during pregnancy*

In six additional cases in which the mother had received no arsenical, the meconium showed no trace of arsenic.

| CASE NUMBER | DATE OF DELIVERY | DURATION OF PREGNANCY | WASSERMANN REACTION | PREVIOUS TREATMENT | ARSENIC IN PLACENTA | ARSENIC IN FOETAL ORGANS | ARSENIC IN MECONIUM |
|---|---|---|---|---|---|---|---|
| | | | | | *mmg. per 100 gr.* | *mmg. per 100 gr.* | *total mmg.* |
| 1 | 4–19 | Term 3,220* | Neg. | Arsph. 0.3. Dec. 27, 30; Jan. 6, 13, 20, 27; Feb. 3. Arsph. 0.2 April 7. | 50 | ..... | 75 |
| 2 | 4–28 | Term 3,195 | Pos. | Arsph. 0.3. March 16; April 6, 13, 24. | 120 | ..... | 90 |
| 3 | 5–2 | Term 3,460 | Neg. | Diarsonal—17 doses. Nov. 17 to April 21. | 40 | ..... | 40 |
| 4 | 5–3 | Term 3,270 | Pos. | Arsph. 0.3. Nov. 8, 16, 23, 30; Dec. 7, 28; Jan. 4, 11; March 24; April 5. | None | ..... | 30 |
| 5 | 5–7 | 7½ Mos. 1,470 | Pos. | Neo-arsph. 0.3. April 20. Arsph. 0.2. April 27; May 4. | 100 | Liver none. Kidney none. | 10 |
| 6 | 5–10 | Term 3,275 | Pos. | Arsph. 0.2. Nov. 23; Dec. 1, 7, 14, 28; Jan. 4, 18, 26. | None | ..... | 10 |
| 7 | 5–11 | Term 3,500 | Pos. | Neo-arsph. 0.6. Feb. 18. Arsph. 0.3. Feb. 23; March 1, 8, 15, 22, 29; April 12. | 50 | ..... | 65 |
| 8 | 5–19 | 9 Mos. 2,780 | Pos. | Neo-arsph. 0.6 Feb. 11. Arsph. 0.3. Feb. 16, 23; March 2, 9, 16, 23; Arsph. 0.2. March 30; April 6, 20, 27. | None | ..... | 55 |
| 9 | 5–24 | Term 3,765 | Pos. | Arsph. 0.3. Feb. 13, 20, 27; March 6, 13, 20, 27; April 3, 10, 17; May 22. | 120 | ..... | 32 |
| 10 | 5–29 | Term 2,650 | Pos. | Arsph. 0.3. Nov. 14, 21, 28; Dec. 5, 12; Neo-arsph. 0.45. Feb. 6, 13, 20, 27; March 6. Arsph. 0.3. May 11, 15, 22. | 40 | Liver 120. Kidney none. | 25 |
| 11 | 5–13 | 5 Mos. 300 | Pos. | Arsph. 0.3. May 10. | 60 | Liver 20 | .. |

* Weight of baby.

on the maternal surface of the chorionic villi; that arsenic in some form is deposited in that region following arsphenamine therapy has already been shown (1). Under such circumstances, it seems barely conceivable that the foetal blood in passing through these chorionic villi might absorb infinitesimal quantities of the arsenic compound there present; this seems somewhat more likely when one learns that the decomposition products of arsphenamine are more diffusible than the drug itself (8). If such an hypothesis be true, the quantities of arsenic in the foetal circulation at any one time would be very small and might well be of magnitudes less than 5 mmg. per 100 cc. of blood, so that their chemical identification would be difficult if not impossible.

## CONCLUSIONS

1. Following the intravenous administration of arsphenamine and neo-arsphenamine to pregnant women, no arsenic is demonstrable in the foetal blood, although large quantities may be present in the maternal circulation.

2. In the meconium of new-born infants, arsenic is constantly present in those cases in which the mothers have had arsphenamine therapy during pregnancy.

3. Following arsphenamine treatments during pregnancy arsenic does not pass from mother to foetus by a process of simple diffusion, but is transmitted in minute quantities by some other mechanism.

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